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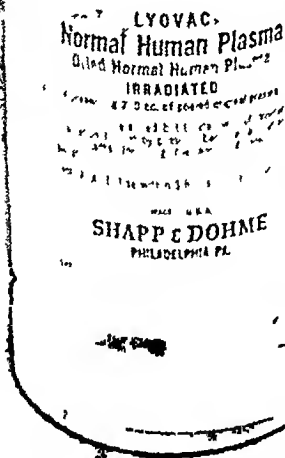


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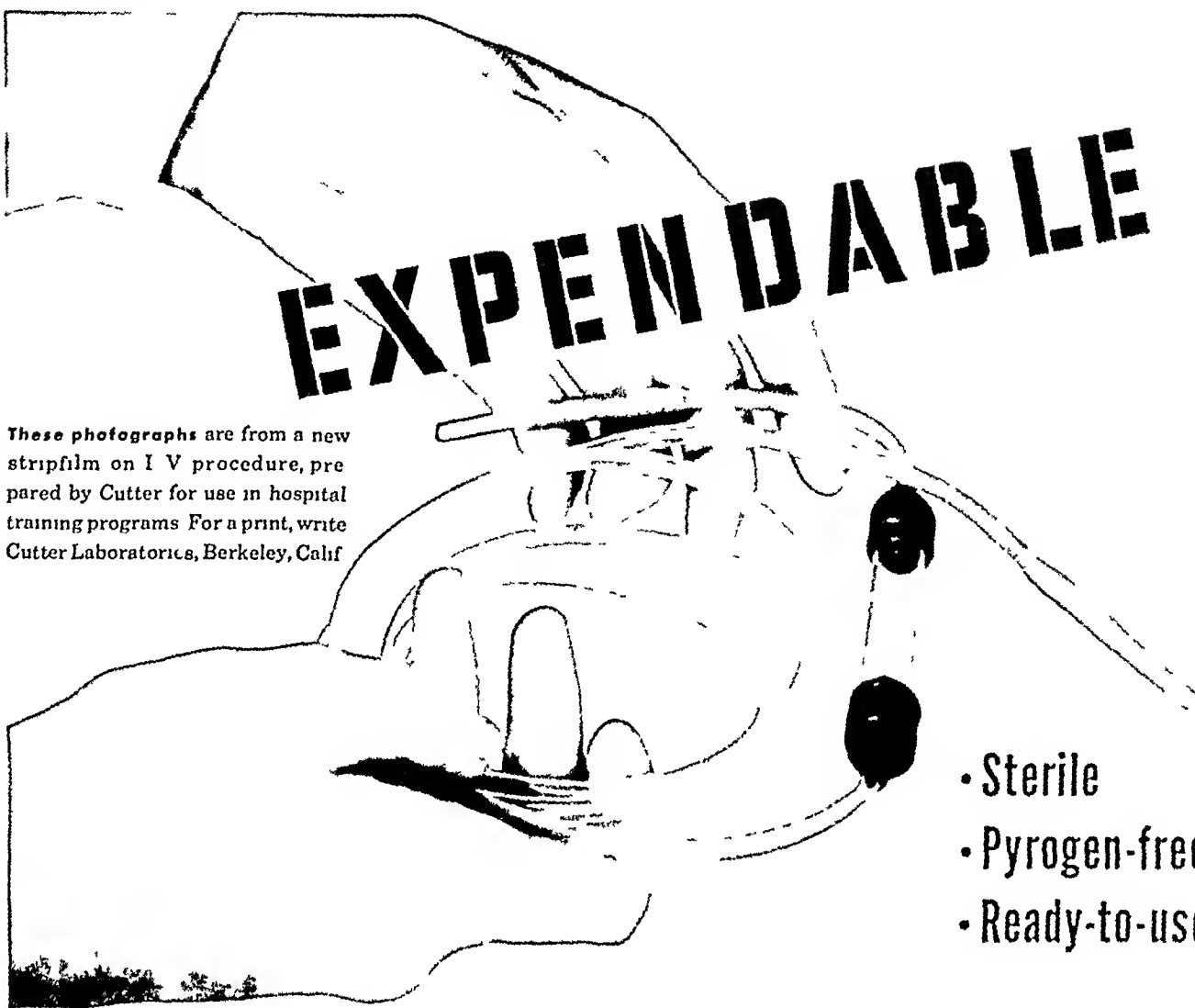
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No 1

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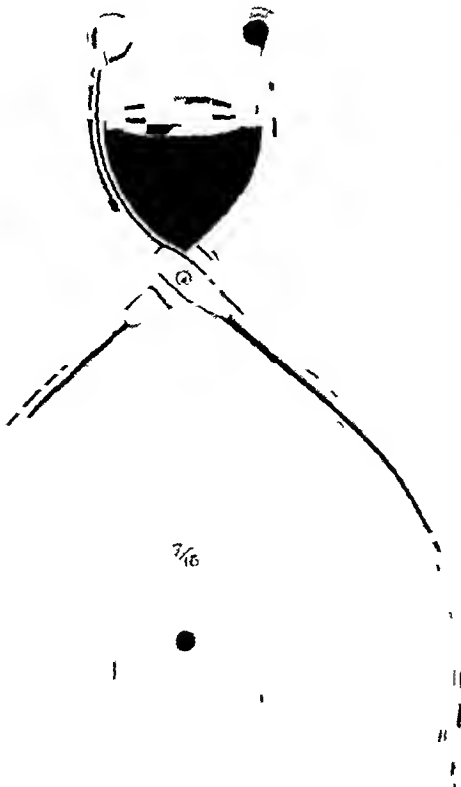
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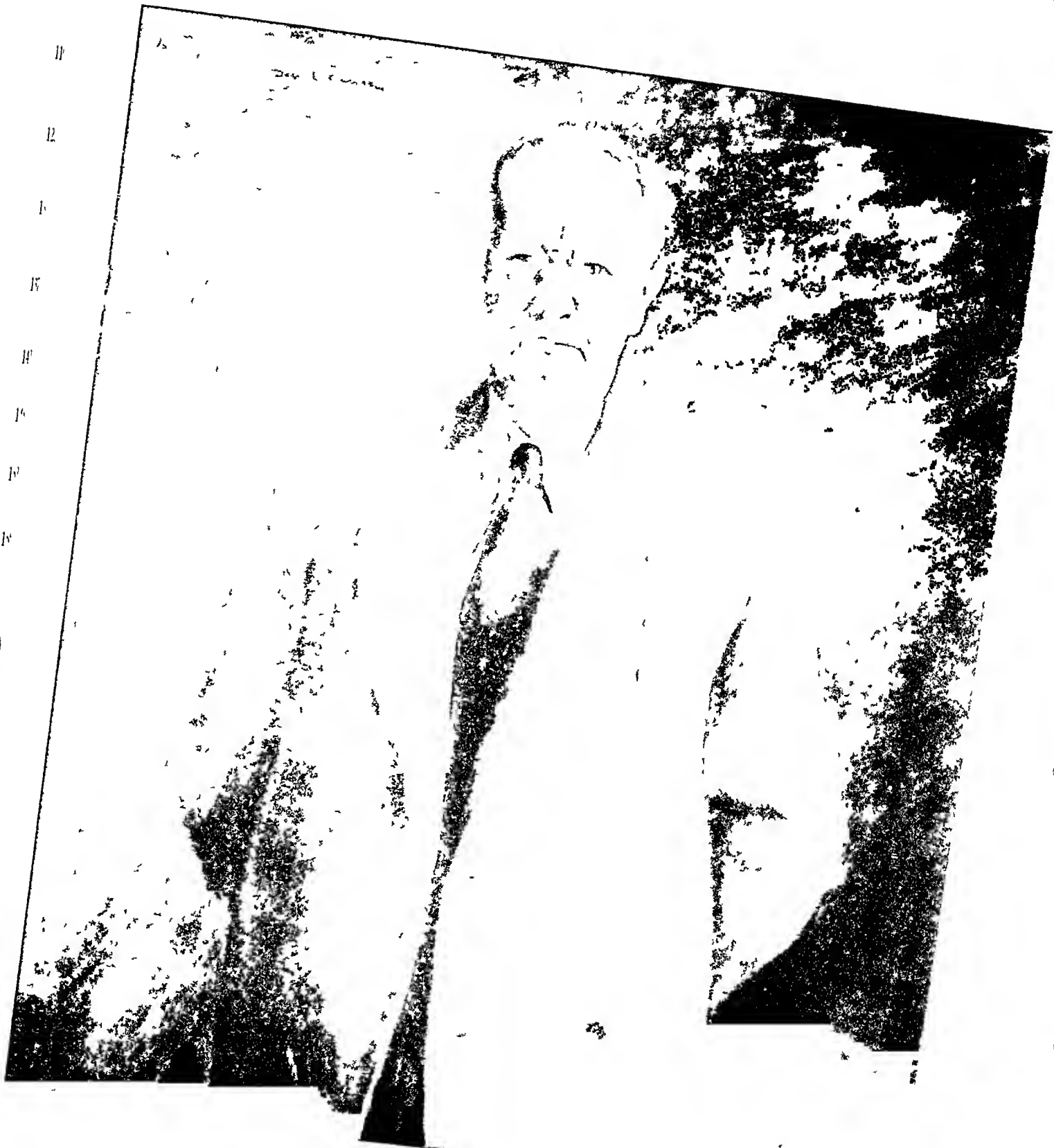
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IN THE FRIENDLY ENTRANCE to the Graduate Hospital of the University of Pennsylvania on December 21st a group of officers of the Hospital, officers of the University of Pennsylvania, professional colleagues, some grateful patients and a small company of close friends of Doctor Walter Estell Lee met to witness the unveiling of a life-size oil portrait by the distinguished artist, Daniel Garber

This fine homage to the surgical eminence of Doctor Lee in Philadelphia is the gift of a group of his admirers and fellow workers. The excellent history of the several hospital services which have had the advantage of his energetic leadership and his work as Recorder of the American Surgical Association, was stimulatingly described by Doctor Jonathan E. Rhoads who made the presentation. His enumeration of Doctor Lee's various offices, his many positions of trust, made such a formidable list. Chesterfield must have whispered into Doctor Lee's ear, "Never put off till tomorrow what can be done today."

The spirit of this occasion could not restrict itself to any recital of accomplishments, but also was a vivid experience keenly felt by those who were a part of this pleasant ceremony. A sense of gratefulness to Doctor Lee and to his wife for her years of devotion to the details of his daily life sank deep into the consciousness of his colleagues and friends, all of whom rejoice in this tribute to his services to American surgery.

The *Annals of Surgery* adds its note of thanks for his editorial dedication to the enlargement of its usefulness and rejoices in the happy accomplishment of this friendly concern of his many admirers.

ELLIS W. BACON

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ANNALS OF SURGERY

VOL 129

JANUARY, 1949

No 1



RESPONSE TO PARENTERAL GLUCOSE OF NORMAL KIDNEYS AND OF KIDNEYS OF POSTOPERATIVE PATIENTS*†

DONALD R COOPER, M D, VIVIAN IOB, PH D,

AND

FREDERICK A COLLER, M D

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL,
ANN ARBOR MICHIGAN

THE INADVISABILITY OF INFLECTING HEAVY LOADS of sodium chloride upon the early postoperative patient has been pointed out in previous reports^{1, 2} Those studies were based upon data derived from patients undergoing combined abdominoperineal resection of the rectum, who were given infusions of various salt solutions A definite variation from the normal handling of the infused salt loads was demonstrated for these patients It is the purpose of this report to present similar studies using infusions of 5 per cent glucose, in an effort to further clarify the problems connected with the proper hydration of the early postoperative patient

Data are presented of the urinary response to small positive loads of parenteral 5 per cent glucose, 1 to 15 per cent of body weight in normal men and in patients following operations of varying magnitude Infusion studies were carried out in three healthy young men, four patients undergoing herniorrhaphy and five patients undergoing combined abdominoperineal resection for carcinoma of the rectum Rates of excretion of sodium chloride potassium and water, and velocity constants of water were calculated for each of the three groups of subjects

PLAN OF STUDY AND PROCEDURE

The nine patients and three control subjects were unselected However, they presented no evidence of gross cardiovascular and kidney disease The patients undergoing combined abdominoperineal resection were prepared for operation by sulfasuxidine, and a high protein high carbohydrate, low residue diet They were transfused before operation when necessary to bring the hemoglobin to 14 Gm per cent The preanesthetic medication was morphine in combination with a barbiturate The operations, with a single exception were performed under spinal anesthesia, using nupercaine or continuous procaine Ether was employed in one instance

* Submitted for publication June 1948

† This work was aided by a grant of the John Harper Society for Medical Surgical Research

All fluid was administered by the intravenous route, in volumes of 750 ml at the rate of 6ml/min every six hours for four or five periods. The three controls received the infusions at the same rate and at the same clock times as the patients. No anesthesia was given in the case of the controls. The methods and procedures followed were those outlined in detail in the earlier paper^{2*}

RESULTS

A representative subject from each group, that is, one control, one from the herniorrhaphy group, and one of the combined resections was chosen for the presentation and comparison of complete data in Tables I and II. For convenience these groups in the above order will be referred to hereafter as Groups I, II and III.

TABLE I—*Blood and Serum Changes in Parenteral 5 Per Cent Glucose*

Subject	Whole Blood			Serum				
	Specific Gravity	Hemo-globin Gm %	Hema-tocrit Vol %	Specific Gravity	Protein Gm %	CO ² mM/L	Na mM/L	Cl mM/L
To—Male control age 22 yrs, 70.8 kg 3000 ml 5% glucose in 24 hours	(1) 1.0578	15.7	45.3	1.0256	6.21	25.2	138.9	104.3
	(2) 1.0581	16.6	53.0	1.0265	6.52	25.8	139.1	98.5
Hu—Female herniorrhaphy age 41 yrs, 70.5 kg 3750 ml 5% glucose in 30 hours	(1) 1.0531	14.1	45.0	1.0221	5.00	26.8	138.0	105.3
	(2) 1.0551	14.2	48.6	1.0243	5.76	26.6	134.8	101.0
B1—Female combined abdominal-perineal resection age 69 yrs 49.6 kg 3750 ml 5% glucose in 30 hours	(1) 1.0524	13.0	41.5	1.0257	6.24	25.8	134.9	102.8
	(2) 1.0506	12.5	42.4	1.0240	5.66	25.4	123.0	94.0

(1) Before infusion and/or operation
(2) At end of infusion period

The whole blood and serum changes for these representative subjects are shown in Table I in which the preoperative and post-infusion findings are compared. It is interesting to note that in the control subject each post-infusion determination with the exception of the serum chloride revealed either an increased concentration of the constituent being measured, or, as in the case of the specific gravity, an indication of increased density of the entire blood sample. Although these changes are minimal they serve to indicate a

* Urines collected during each six-hour period were preserved by addition of 1 ml of 12.8 per cent Zephiran and kept in the refrigerator. They were analyzed for pH, Na, K, NH₃, PO₄, SO₄, titratable acidity to pH 7.4, Cl, total nitrogen, urea nitrogen and creatinine. In one patient urinary calcium³ and magnesium⁴ were also determined. Losses of both elements were exceedingly small, amounting to approximately 1 milliequivalent per 24 hours.

Two blood samples, one under oil and one with heparin, were withdrawn before operation and at the end of the infusion period. Hemoglobin, volume of red cells, and whole blood specific gravity were determined in the heparinized samples, CO₂, Na, Cl and serum proteins in the serum.

general tendency, in that they are uniformly in the same direction. They are perhaps more indicative when compared to the subject from Group III. Here all the changes are in the opposite direction with the exception of the hematocrit, which shows little change. The figures for the patient undergoing herniorrhaphy seem to fall midway between Groups I and III. It thus appears that there is a tendency toward hemoconcentration in Group I and hemodilution in Group III with Group II showing little change.

The detailed urinary findings on these same three individuals are presented in Table II. The findings in the control subject appear to be typical

TABLE II.—*Composition of Urine, mEq Per Liter*

Period	Vol ml	pH	Specific Grav ity	K mEq	Na mEq	NH ₃ mEq	Cl mEq	SO ₄ mEq	PO ₄ mEq	Tit Acid mEq	Tot N Gm/L	Urea N Gm/L	Creati- nine Gm/L
Control To Male—weight loss 1.50 kg													
Urine in bladder		5.95	1.009	48.0	91.0	24.7	90.3	41.3	28.5	22.6	10.407	9.301	1.250
0-6th hr	938	6.09	1.006	29.1	44.2	9.3	59.4	10.2	9.7	8.6	4.538	3.994	0.600
6-12th hr	1120	6.58	1.005	8.8	37.4	6.5	34.8	6.3	6.9	3.4	2.519	2.100	0.388
12-18th hr	590	5.95	1.004	18.9	10.7	11.6	15.5	6.2	10.7	12.4	4.180	3.484	0.750
18-24th hr	500	6.03	1.003	18.9	4.4	12.4	6.3	5.5	11.6	13.2	4.123	3.416	0.913
Patient Hu Female herniorrhaphy—weight loss 1.25 kg													
12 ^o preop	1315	6.61	1.009	44.9	109.8	11.1	99.5	25.4	19.5	14.1	5.714	4.997	0.739
0-6th hr	530	7.02	1.004	31.3	47.9	6.8	49.0	7.1	14.2	6.0	2.969	2.454	0.491
6-12th hr	299	7.37	1.004	36.2	63.5	7.9	45.8	11.4	15.8	5.0	3.697	3.409	0.729
12-18th hr	415	5.52	1.005	32.4	11.1	19.5	14.0	12.9	26.6	54.1	4.090	3.515	0.845
18-24th hr	840	5.93	1.002	13.7	6.5	8.1	12.3	6.2	7.5	17.5	2.885	2.658	0.420
24-30th hr	1145	6.38	1.001	9.0	8.9	1.5	8.1	3.3	6.1	9.2	1.849	1.554	0.289
Patient B1 Female combined abdominoperineal resection													
12 ^o preop	800	5.52	1.007	33.0	97.4	9.4	140.8	24.1			5.502	4.261	0.547
0-6th hr	100	5.35	1.016	96.1	56.8	17.1	114.3	23.2	38.7	24.9	5.836	3.947	0.982
6-12th hr	140	5.28	1.020	79.9	11.8	11.7	38.0	28.8	42.9		7.170	5.786	1.061
12-18th hr	65	5.48	1.019	73.4	0.7	54.4	24.5	42.7	80.1		13.423	10.465	2.722
18-24th hr	380	6.05	1.002	11.3	0.8	12.0	8.4	7.2	19.0	15.4	3.974	3.401	0.579
24-30th hr	542	6.10	1.001	7.2	1.2	10.9	6.5	3.9	9.4	23.2	2.334	1.805	0.347

of the expected water diuresis in a normal adult. The urine volume is excessive for the first two periods following which it rapidly diminishes as the water is conserved by the kidneys. Excretion of sodium and chloride is also relatively large in the first two periods, but apparently those ions are also conserved in the last 12 hours since their concentrations are diminished in spite of the much smaller urinary volume. It is further noted that the specific gravity of the urine continues to fall in spite of the decrease in urine volume. The 24-hour urine volume for this subject exceeded by 148 ml the total infusion and he lost 1.5 kg in weight.

Patients Hu and B1 are found to differ to a considerable extent from the control. The former experienced no diuresis until the fourth period and her largest output was found in the fifth period. Throughout the five periods, however, her urine volume totaled only 521 ml less than the volume of the infused solution. She lost 1.25 kg in body weight. Patient B1 could never be

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6-12th hr	1120	6.58	1.005	8.8	37.4	6.5	34.8	6.3	6.9	3.4	2.519	2.100	0.388
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18-24th hr	840	5.93	1.002	13.7	6.5	8.1	12.3	6.2	7.5	17.5	2.885	2.658	0.420
24-30th hr	1145	6.38	1.001	9.0	8.9	1.5	8.1	3.3	6.1	9.2	1.849	1.554	0.289
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6-12th hr	140	5.28	1.020	79.9	11.8	11.7	38.0	28.8	42.9		7.170	5.786	1.061
12-18th hr	65	5.48	1.019	73.4	0.7	54.4	24.5	42.7	80.1		13.423	10.465	2.722
18-24th hr	380	6.05	1.002	11.3	0.8	12.0	8.4	7.2	19.0	15.4	3.974	3.401	0.579
24-30th hr	542	6.10	1.001	7.2	1.2	10.9	6.5	3.9	9.4	23.2	2.334	1.805	0.347

of the expected water diuresis in a normal adult. The urine volume is excessive for the first two periods following which it rapidly diminishes as the water is conserved by the kidneys. Excretion of sodium and chloride is also relatively large in the first two periods, but apparently those ions are also conserved in the last 12 hours since their concentrations are diminished in spite of the much smaller urinary volume. It is further noted that the specific gravity of the urine continues to fall in spite of the decrease in urine volume. The 24-hour urine volume for this subject exceeded by 148 ml the total infusion and he lost 1.5 kg in weight.

Patients Hu and Bi are found to differ to a considerable extent from the control. The former experienced no diuresis until the fourth period and her largest output was found in the fifth period. Throughout the five periods, however, her urine volume totaled only 521 ml less than the volume of the infused solution. She lost 1.25 kg in body weight. Patient Bi could never be

said to have experienced any diuresis, the largest urine volume being only 42 ml in excess of the smallest volume excreted by the control. This patient was oliguric throughout the first three periods studied, and her total urine volume for the study was 2523 ml less than the volume of fluid infused.

The concentration of the sodium and chloride ions in the urine of patients Hu and B₁ approximated closely those found for the controls. The actual output, however, of these ions, as well as the other urinary constituents in the table, expressed either in total quantity or in excretion rates per hour, varied greatly from the control as will be found in succeeding tables.

An interesting finding for patient B₁ is the slight increase in the specific gravity of the urine during the periods of oliguria. These determinations of specific gravity for B₁ were representative of this group of patients as well as of other similar groups studied (see Tables VI and VII). There were how-

TABLE III—*Parenteral 5 Per Cent Glucose Cumulative Data Water Potassium and Salt, Controls*

			Urine Composition				Urine Excretion Rate				Water Load*	1/Δt	Serum Composition	
			Water	Potas- sium	Sodi- um	Chlo- ride	Water	Potas- mM	So- dium	Chlo- ride			Sodi- mM	Chlo- ride
Controls	Period hr	ml	mM	mM	mM	ml/hr	/hr	/hr	/hr	ml	hr	/ml	/ml	
Th Male	0-6th	1408	28.5	53.1	46.1	234.7	4.8	8.9	7.7	-923	-0.250	0.141	0.095	
Age 26 yrs	6-12th	2148	34.9	92.5	74.7	123.3	1.1	6.6	4.8	-1191	-0.104			
Wt loss	12-18th	2808	39.5	105.4	84.9	110.0	0.8	2.2	1.7	-1384	-0.080			
176 kg	18-24th	3528	45.7	110.6	95.6	120.0	1.0	0.9	1.8	-1637	-0.073	0.139	0.098	
To Male	0-6th	938	27.3	41.5	55.7	157.6	4.6	6.9	9.3	-385	-0.409	0.139	0.104	
Age 22 yrs	6-12th	2058	37.2	83.4	94.7	186.7	1.7	7.0	6.5	-976	-0.191			
Wt Loss	12-18th	2648	48.3	89.7	103.9	98.3	1.9	1.1	1.5	-1043	-0.094			
15 kg	18-24th	3148	57.7	91.9	107.1	83.3	1.6	0.4	0.5	-1028	-0.081	0.139	0.099	
Ta Male	0-6th	610	19.7	25.0	39.1	101.7	3.3	4.2	6.5	-88	-1.155	0.138	0.101	
Age 24 yrs	6-12th	1406	27.0	59.6	70.8	132.7	1.2	5.8	5.3	-397	-0.334			
Wt Loss	12-18th	1891	34.8	69.2	83.1	80.8	1.3	1.6	2.1	-370	-0.218			
0.59 kg	18-24th	2359	40.4	73.5	90.7	78.0	0.9	0.7	1.3	-346	-0.225	0.139	0.098	

* Water load corrected for insensible loss and oxidative gain estimated from glucose infused and urinary nitrogen.

ever, two patients (He and Sch, Table V) whose urinary specific gravity findings varied distinctly from the majority. These two patients revealed urinary specific gravities ranging between 1.028 and 1.035 throughout the entire study and the possibility of pre-existing and/or continuing dehydration was considered. In other data to be presented (Table V) further variations in the urinary excretion of these two patients are noted as compared to the other patients in Group III. It is of some interest that He and Sch are comparatively young men in contrast to the three elderly women who underwent similar operative procedures.

The individual cumulative data of urinary composition and the excretory rates for water, potassium, sodium and chloride for all subjects are contained

in Tables III, IV and V The calculated water load was corrected for insensible loss, oxidative gain from glucose combusted and water freed from destroyed tissue *

TABLE IV—*Parenteral 5 Per Cent Glucose Cumulative Data Water, Potassium and Salt, Hemorrhaphy*

Patient	Period hr	Urine Composition				Urine Excretion Rate				Water Load* ml	1/ Δ t hr	Serum Composition	
		Water ml	Potassium mM	Sodium mM	Chloride mM	Water ml/hr	Potassium mM/hr	Sodium mM/hr	Chloride mM/hr			Sodium mM/ml	Chloride mM/ml
Do Male Age 46 yrs 77.3 kg	0-6th	192	7.3	26.4	23.3	32.0	1.2	4.4	3.9	217	0.148	0.134	0.100
	6-12th	446	22.4	62.7	56.2	42.3	2.5	6.1	5.5	449	0.094		
	12-18th	984	41.7	102.0	101.1	89.7	3.2	6.6	7.5	419	0.214		
	18-24th	1904	54.1	130.8	133.7	154.0	2.1	4.8	5.4	-18	-9.111		
	24-30th	2706	67.5	159.1	164.5	133.7	2.2	4.1	5.1	-337	-0.397	0.135	0.095
Ho Male Age 54 yrs 70 kg Wt Loss 1.6 kg	0-6th	229	21.2	43.8	54.0	49.5	3.5	7.3	9.0	297	0.167	0.140	0.106
	6-12th	504	31.3	84.8	97.4	45.8	1.7	6.8	7.2	526	0.087		
	12-18th	909	48.0	120.5	142.2	67.5	2.8	6.0	7.5	634	0.107		
	18-24th	1152	62.5	133.1	166.4	40.5	2.4	2.1	4.0	892	0.045		
	24-30th	1787	69.8	144.5	183.8	105.8	1.2	1.2	2.9	746	0.142	0.135	0.101
Hy Male Age 63 yrs 56 kg	0-6th	168	11.1	12.9	22.2	28.0	1.9	2.2	3.7	396	0.071	0.136	0.100
	6-12th	286	20.1	21.9	36.9	19.7	1.5	1.5	2.5	831	0.024		
	12-18th	866	32.6	34.6	57.6	96.7	2.1	2.1	3.5	828	0.117		
	18-24th	2181	40.7	49.1	78.5	219.2	1.4	2.4	3.5	81	2.706		
	24-30th	3145	47.9	60.3	93.9	160.7	1.2	1.9	2.6	-191	-0.841	0.131	0.095
Hu Female Age 41 yrs 70.5 kg Wt Loss 1.3 kg	0-6th	530	16.9	25.4	25.5	88.3	2.8	4.2	4.3	-39	-2.260	0.138	0.105
	6-12th	829	27.7	44.4	39.2	49.8	1.8	3.2	2.3	145	0.343		
	12-18th	1244	41.2	49.0	45.0	69.2	2.3	0.8	1.0	224	0.309		
	18-24th	2064	52.7	54.4	55.3	140.0	1.9	0.9	1.7	-110	-1.273		
	24-30th	3209	63.1	64.6	64.6	190.8	1.7	1.7	1.6	-775	-0.253	0.136	0.101

* Water load corrected for insensible loss and oxidative gain estimated from infused glucose and urinary nitrogen

The concentrations of sodium and chloride in the serum, before and at the conclusion of the infusion periods, are included in these tables to emphasize once again the variation in the three groups. A tendency toward equal pre- and post-infusion levels is found in Group I. There is a definite trend, however, in Group III toward a decreased concentration of these ions in the post-infusion samples.

* The water freed by tissue destruction was estimated from urinary nitrogen by use of the factor 6.25, the water gained equalling 0.27 liters per 100 Gm protein.⁵ Insensible loss was estimated as 0.07 per cent of body weight per hour.⁶ Thus the total water load equalled the infused fluid, plus water freed by combustion of glucose and destruction of tissue, minus urinary water and insensible loss.

The velocity constants for water excretion are also included in these tables. These are calculated (after the method of Wolf⁷) by dividing the average rate of excretion during the six-hour period by the load at the end of the period.

TABLE V—*Parenteral 5 Per Cent Glucose Cumulative Data Water, Potassium and Salt, Combined Abdominoperineal Resections*

Patient	Period hr	Urine Composition				Urine Excretion Rate				Water Load* ml	1/Δt -1 hr	Serum Composition	
		Water ml	Potas- sum mM	Sodi- um mM	Chlo- ride mM	Water ml/hr	Potas- sum mM/hr	So- dium mM/hr	Chlo- ride mM/hr			Sodi- um mM/ml	Chlo- ride mM/ml
He Male	0-6th	50	5.9	4.7	6.0	8.3	1.0	0.8	1.0	426	0.020	0.136	0.102
Age 23 yrs	6-12th	133	19.2	8.8	15.1	13.8	2.2	0.7	1.5	823	0.017		
70 kg	12-18th	293	51.5	15.1	29.8	26.7	5.4	1.1	2.5	1165	0.023		
	18-24th	563	87.5	29.8	48.1	45.0	6.0	2.5	3.1	1424	0.032		
	24-30th	877	123.2	57.2	67.1	52.3	6.0	4.6	3.2	1650	0.032	0.123	0.091
Sch Male	0-6th	417	10.4	20.6	16.0	69.3	1.7	3.6	2.7	48	1.440	0.134	0.099
Age 41 yrs	6-12th	687	55.1	47.4	27.0	45.0	7.5	4.5	1.8	158	0.285		
79.5 kg	12-18th	905	90.3	74.2	35.4	36.3	5.7	4.5	1.4	410	0.089		
	18-24th	1088	118.5	96.9	43.8	30.5	4.8	3.8	1.4	596	0.051		
	24-30th	1373	147.5	117.1	56.5	47.5	4.8	3.4	2.1	806	0.059	0.121	0.092
Ro Female	0-6th	64	5.6	6.1	7.5	10.7	0.9	1.0	1.3	445	0.024	0.133	0.107
Age 56 yrs	6-12th	234	22.3	21.0	23.5	28.3	2.8	2.5	2.7	798	0.036		
61.4 kg	12-18th	406	34.5	24.9	31.6	28.7	2.0	0.7	1.4	1151	0.025		
	18-24th	1266	44.4	27.9	38.5	143.3	1.7	0.5	1.2	818	0.175		
	24-30th	1898	53.8	31.8	48.9	105.3	1.6	0.7	1.7	717	0.147	0.130	0.097
Cu Female**	0-6th	200	5.2	10.6	12.4	33.3	0.9	1.8	2.1	312	0.107	0.139	0.111
Age 53 yrs	6-12th	405	12.5	14.1	19.7	34.2	1.2	0.6	1.2	626	0.055		
61.6 kg	12-18th	575	19.3	16.1	28.0	28.3	1.1	0.3	1.4	953	0.030		
Wt gained	18-24th	715	23.8	17.8	37.9	23.3	0.8	0.3	1.7	1340	0.017		
0.7 kg	24-30th	907	30.6	19.9	52.4	32.0	1.1	0.4	2.4	1672	0.019	0.134	0.097
B1 Female	0-6th	100	9.6	5.7	11.4	16.7	1.6	1.0	1.9	463	0.036	0.135	0.103
Age 69 yrs	6-12th	240	20.7	7.4	16.7	23.3	1.9	0.3	0.9	892	0.026		
49.6 kg	12-18th	305	25.5	7.5	18.3	10.8	0.8	0.0	0.3	1395	0.008		
	18-24th	685	29.8	7.8	21.5	63.3	0.7	0.1	0.5	1594	0.040		
	24-30th	1227	33.7	8.5	25.0	90.3	0.7	0.1	0.6	1627	0.056	0.123	0.094

* Water load corrected for insensible loss and oxidative gain estimated from glucose infused and urinary nitrogen

** Ether anesthesia colostomy, inoperable carcinoma of rectosigmoid

For clearer visualization of the variations demonstrated by these three groups of patients in the handling of the infusions, postoperative rates of urinary excretion for each group have been averaged and compared graphically in Figure 1. Although the averages in each instance include a relatively small series of cases, the trends for each group seem quite definite.

The rates of urinary excretion for water, sodium and chloride are illustrated in Sections A and B. The diuresis is again noted for the control group in the first two infusion periods. This is accompanied by a relatively high excretion rate of sodium and chloride until the third and fourth periods at which time both sodium and chloride are more adequately conserved. The Group III patients, on the other hand, reveal very low excretion rates of water and salt throughout the entire study. The highest rate of water excretion, as attained in the fourth and fifth periods, was less than two-thirds the

lowest value recorded for the controls. The excretion rate of sodium represented a flat curve throughout the entire study. The course of the herniorrhaphy group was again found midway between Groups I and III. These patients followed an initial 12-hour oliguria with a pronounced diuresis in the last two to three periods. The rate of sodium excretion, however, was greater during the oliguria than it was during the last two periods when very dilute urine was being excreted.

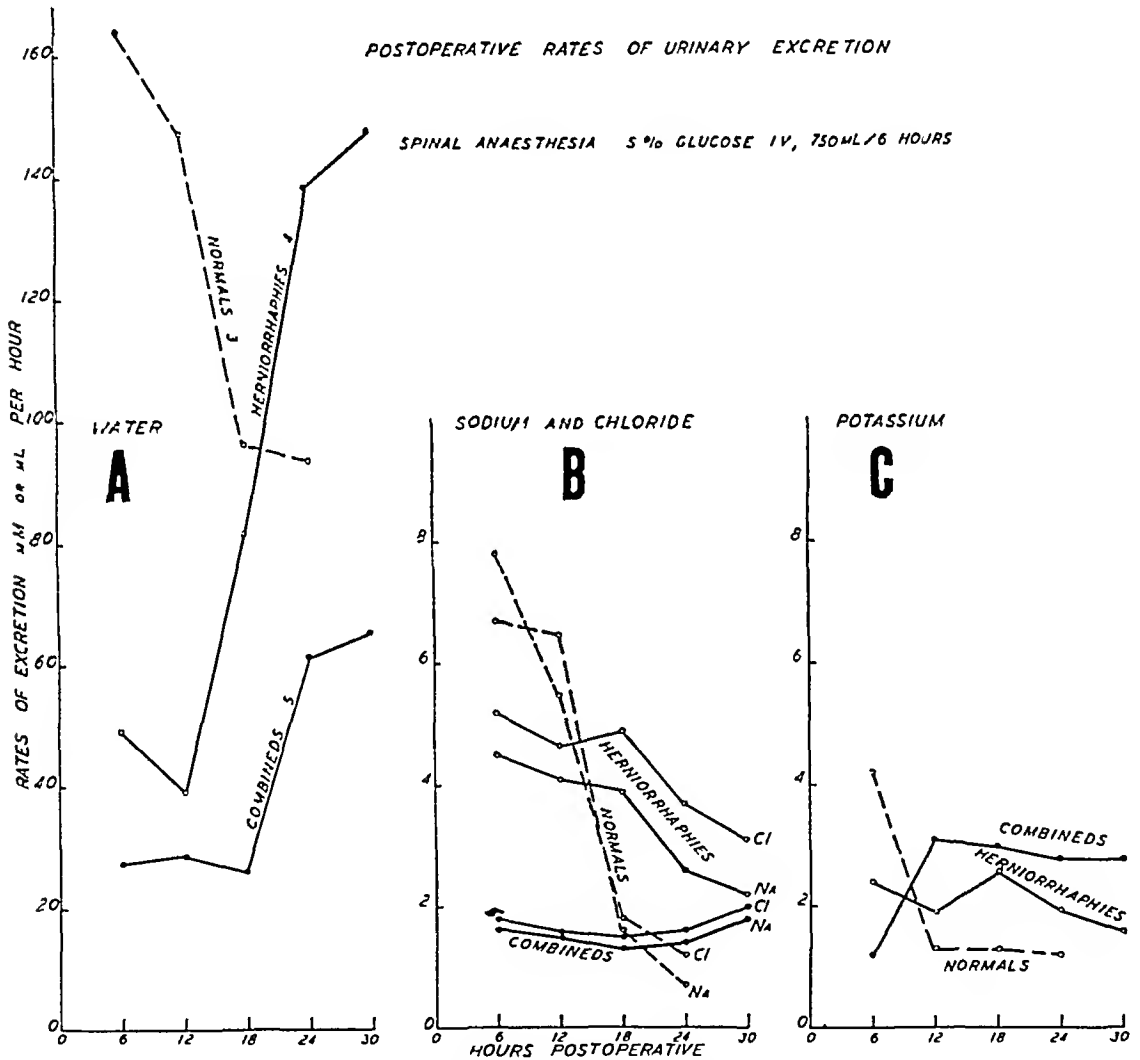


FIG 1—Average postoperative rates of urinary excretion of water, sodium, chloride and potassium plotted against time for normal men (3), patients undergoing herniorrhaphy (4) and combined abdominoperineal resection (5)

The urinary excretion rates of potassium for these patients are found in Section C. This factor, however interesting, is being discussed independently in another communication.

DISCUSSION OF RESULTS

Infusions of 5 per cent glucose given in the dosages described above are apparently handled differently by each of the three groups of patients studied. The solution produced dehydration uniformly in the control subjects as a

result of an initial diuresis and salt loss not completely compensated during the 24 hour study. The tendency in the hemorrhaphy group was toward only slight dehydration, the diuresis occurring after 12 to 18 hours and being simultaneous with a decreased rate of sodium excretion. The excretion of both water and salt remained low throughout the study of patients undergoing combined abdominoperineal resection of the rectum. This resulted in a positive water load at the conclusion of the study on these patients. The most striking contrast in urinary output between the control group and the two operated groups occurred in the first six postoperative hours.

Two interesting questions are posed by the above results. (1) What are the reasons for the variations in the handling of these infusions by the three groups studied, and (2) what is the clinical significance?

No single answer to the first question would seem possible when one considers all the possibilities and complexities involved. It does seem reasonable, however, to rule out some of the more obvious explanations by means of additional data acquired in further investigations.

The initial oliguria, most pronounced in the Group III patients, makes necessary the consideration of possible preoperative dehydration as a causative factor. Certainly the hydration previous to these studies could not be absolutely controlled. All patients however were able to take adequate nutrition by mouth preoperatively and were felt clinically to be optimally prepared for their surgical procedures. Furthermore, the control group as well as the two operated groups was deprived of all food and fluid for 12 hours before the study.

It would appear from Figure 1, Sections A and B, that the more extensive the operation, the more severe and prolonged is the immediate postoperative oliguria. It might thus be postulated that the oliguria is a result of excessive fluid losses at operation, such as operative hemorrhage or fluid lost into the wound. Further operative losses would include the possibility of a greater insensible water loss during the procedures of greater magnitude, or increased loss through perspiration. No allowance was made for these factors in the water loads calculated. In considering either preoperative or operative dehydration as factors influencing the oliguria found in these patients, reference is again made to the determinations of urinary specific gravity. If a high urinary specific gravity can be used as an index of dehydration, only two of the Group III patients (He and Sch) may be considered as dehydrated on this basis.

To explore the possibility of dehydration more thoroughly, some data were collected on two further groups of patients. In one group of six patients undergoing combined abdominoperineal resection of the rectum (Group IV), blood transfusions were given in the first six postoperative hours in addition to the 750 ml of 5 per cent glucose as given previously. The blood was given during the operation, usually as a prophylactic measure, and in the amounts calculated by the operating surgeon as adequate replacement for the blood lost. The infusions in Group IV, therefore, differed from those in Group

III only in that blood losses were adequately replaced in the former. The oligurias demonstrated in the first six postoperative hours (Table VI) and the specific gravities of the urines for these two groups are similar in spite of the variation in blood administered.

TABLE VI—*Parenteral 5 Per Cent Glucose and Blood Intake, Output and Urinary Specific Gravity Combined Abdominopelvic Resections*

Patient	Hours Postop	Intake in ml		Output in ml	
		Blood	5% Glucose	Urine	Specific Gravity
R ₁	0-6	400	750	125	1.015
Male	6-24		2250	235	1.011
61 yrs	24-30		750	72	1.012
W ₁	0-6	900	750	123	1.013
Male	6-24		2250	535	1.008
47 yrs	24-30		750	550	1.005
W ₂	0-6	900	750	100	1.022
Male	6-24		2250	1205	1.019
70 yrs	24-30		750	515	1.005
G ₁	0-6	1000	750	125	
Female	6-24		2250	1435	1.003
20 yrs	24-30		750	290	1.007
M ₁	0-6	500	750	85	1.022
Male	6-24		2250	515	1.018
54 yrs	24-30		750	95	
F ₁	0-6	500	750	145	1.013
Male	6-24		2250	360	
60 yrs	24-30		250	580	1.005

In a fifth group (Group V) the urinary output was carefully recorded, but the fluid intake was left to the discretion of the staff in charge. These patients received their required blood transfusions and fluid infusions in one continuous drip, which was started during the operation and was completed within five to eight hours. The intakes and outputs for these patients are found in Table VII.

The infusions for the patients in Group V differed from those in Group III not only in that adequate blood replacement was administered but also as to injection times. Consequently, large volumes of fluid were administered during the period of oliguria. The urine volumes, however, were again found to be small in the first six postoperative hours. Patient L_a, for example, received an infusion totalling 3800 ml in the first six hours, and his total urine volume for that period was 55 ml with a specific gravity of 1.008. Whether or not the oliguria found in these patients in the first six hours postoperatively is caused by preoperative or operative dehydration, it can be stated that it is not altered by adequate blood replacement or rapid, massive infusions of fluid.

The anesthetic agent as a contributing cause cannot be ruled out. Although

the majority of the patients studied received a continuous spinal anesthesia, using procaine as the anesthetic agent, it was found that the results were not changed by varying the type of anesthetic employed. Some of the modifications of anesthesia included sodium pentothal as a supplement to the spinal, nitrous oxide-oxygen-ether general anesthesia, and cyclopropane with curare. Previous studies on renal function under anesthesia⁸ have revealed no change in glomerular filtration rate or renal blood flow under the above three anesthetics if the factor of hypotension could be eliminated. It might be noted that the patients undergoing herniorrhaphy in Group II also received procaine spinal anesthesia, although, of course, in a more limited quantity.

TABLE VII—*Early, Continuous Parenteral Infusions Plus Blood Intake, Output and Urinary Specific Gravity, Combined Abdominoperineal Resections*

Patient	Intake in ml					Output in ml			Comment
	Hours Postop	Blood	5% Glucose	Saline	Oral	Hours Postop	Urine	Specific Gravity	
Bo Male 67 yrs	0-8	1500	3000	250		0-6	210		
						6-24	380	1.018	
						24-30	45		
K1 Female 56 yrs	0-8	1000	2600	850		0-9	350	1.015	Ether and curare anesthesia Shock
						9-25	390		
Ge Male 63 yrs	0-7		3000			0-6	250		
						6-24	610		
Ka Male 49 yrs	0-6		3000			0-8	191		Shock at 12 hours postoperatively
	12-15	500		400		8-24	705		
La Male 71 yrs	0-6	1000	2000	800		0-6	55	1.008	Ether anesthesia
						6-24	1305	1.014	
Da Male 52 yrs	0-7	1000	1000	600	200	0-24	1100		Sigmoid resection
P1 Male 40 yrs	0-9	1000	1100	1000	1400	0-24	675		Laparotomy and biopsy cyclopropane and curare anesthesia

The factors of hypotension, shock and cellular anoxia must be considered in evaluating these results. The anesthetic records of all these patients have been carefully studied and only two of them (K1 and Ka) developed the syndrome indicative of surgical shock. Even those patients who received no transfusions remained free from this complication—in fact, had shock developed in one of the latter patients he would have been automatically eliminated from this category, for no transfusions were withheld if the condition of

the patient indicated the need. It cannot be stated, however, that none of these patients showed any transient periods of hypotension, as the majority did develop this complication for a brief interval at some time during the course of the operation. This was usually felt to be a result of the spinal anesthesia and responded well in all instances to one of the vaso-pressor drugs. Although no clinical signs of shock or anoxia developed in these patients, it is of course impossible to obtain any estimation of the amount of compensatory vaso-constriction which may have been present even though the full-blown clinical picture of shock was not evident. Once again, however, it is of interest to note that the results in patients with and without blood replacement were similar.

In attempting to evaluate the degree of clinical significance which might be attached to the data presented, reference may well be made to the average water loads and sodium losses in the original three groups of patients. The average water load, for example, in the control group over the 24 hour study period was — 1003 ml, accompanied by an average sodium loss of 92 mEq. Although this is a loss of water slightly in excess of sodium (as compared to the concentration of extracellular fluid), the excess is not large and is further minimized by the renal conservation of sodium, as shown in the last period when an average of only 3.6 mEq of sodium were excreted in the urine. A salt water deficit is thus present in the control group but is being controlled adequately by normal renal function, even though absolute salt conservation cannot be expected.

The average water load in the hemorrhaphy group over the 30 hour study period is found to be — 139 ml, with an average sodium loss over the same period of 107 mEq. These patients then have lost salt in excess of water. This change involves less than one liter of extracellular fluid during the first 30 postoperative hours and is being well compensated in the last study period at which time water is being excreted in excess of sodium (887 ml of water and 15.3 mEq of sodium). In this group, then, there is small but definite derangement of body fluids in the first 12 postoperative hours, which is held in check when compensation is begun through more adequate renal function in the last two periods.

In the patients undergoing combined abdominoperineal resection, a positive water load averaging 1300 ml is found for the first time at the end of the 30-hour study period. At the same time the sodium loss, though minimal, is present and averages 47.3 mEq over the 30 hour period. Here, then, is the only group whose averages reveal a positive water load with a negative sodium load. Renal compensation in the latter part of the study which was evident in the first two groups is minimal for these patients as noted by the curves in Figure 1, Sections A and B. It is further noted that small amounts of sodium excreted by these patients throughout the first two postoperative periods are apparently not the result of renal conservation of salt, but rather a function of the small quantities of urine produced, for, as shown in Table II the concentration of salt in the urine of one of these patients closely approxi-

mated that of the representatives of the other two groups. The pre- and post-infusion blood studies in Table I confirm the results of these urinary analyses.

It would appear, then, that the administration of 5 per cent glucose solution in the quantities employed in this study should be free of serious derangement of body fluids in normal, healthy persons and in healthy individuals undergoing operations of the magnitude of herniorrhaphy.

In patients undergoing combined abdominoperineal resection of the rectum, renal excretion of both salt and water is apparently quite different from the normal, with urinary volumes greatly depressed in the first six to twelve postoperative hours. The result is a positive load of water accompanied by a small urinary loss of salt, at the same time, evidence of hemodilution is encountered in the blood. These findings appear to be independent of the load of 5 per cent glucose administered and of the rate of administration, and are not affected by the replacement of the blood loss during operation.

It would seem to follow that the administration of intravenous infusions of 5 per cent glucose in these patients should not be "pushed" during the first hours postoperatively, in spite of low urinary output. The practice of starting an intravenous infusion before operation and continuing this infusion at a relatively rapid rate until a 24 hour supply of water has been injected into the patient within the first six to eight postoperative hours seems unjustified. Although frequently no ill effects from this procedure are observed, its practice in the malnourished, chronically ill, elderly patient certainly should increase the danger of such complications as pulmonary edema, wound edema, cardiac failure and water intoxication.

Careful planning in the prescription of 5 per cent glucose infusions in these patients in the immediate postoperative period is as important as in the prescription of saline infusions. The giving of sufficient 5 per cent glucose during this period (6-12 hours) to cover the calculated insensible water loss in addition to transfusions of blood to replace adequately the blood lost would seem to be a logical handling of the situation. Further infusions after the first 12 hours could then be given in amounts calculated for adequate renal requirements.

SUMMARY

Infusions of 5 per cent glucose were administered to three control subjects, four patients undergoing herniorrhaphy and five patients undergoing combined abdominoperineal resection of the rectum. Each individual was given 750 ml of 5 per cent glucose in each of four or five periods of six hours. Excretion rates and loads of water, sodium, chloride and potassium were determined.

The control group revealed an initial diuresis in the first six to twelve hours with accompanying losses of salt. In the third and fourth periods renal conservation brought the excretion of both water and salt to a minimum. The subjects were somewhat dehydrated at the conclusion of the study as indicated by loss of weight and greater losses of water than salt.

The patients undergoing herniorrhaphy experienced, on the average, reduced excretions of water during the first two periods, which changed to a definite diuresis in the later periods. Sodium and chloride were excreted more rapidly during the periods of low water output, but were conserved during the diuresis. These patients lost, on the average, small amounts of salt in excess of water, but again adequate renal compensation was in evidence at the conclusion of the study.

Data from patients undergoing combined abdominoperineal resection of the rectum revealed an oliguria occurring in the first six to 12 postoperative hours, which was associated with minimal output of sodium and chloride throughout the study period. As a result, there was a positive load of water accompanied by a small loss of salt.

Some of the causative factors associated with these differences in the handling of 5 per cent glucose are discussed. Further data are presented which show that the addition of either adequate blood replacement during operation or infusions of large volumes of glucose in the early postoperative period are without influence upon the oligurias noted in those patients undergoing large operations.

During the first six to 12 hours after operation, it is recommended that intravenous infusions be limited to transfusions of blood to replace blood loss and to that amount of 5 per cent glucose required to replace insensible loss of water. After this period, and following a careful evaluation of the patient's state of hydration, sufficient 5 per cent glucose may be infused to support renal function adequately.

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APPRAISAL OF ORAL STREPTOMYCIN AS AN INTESTINAL ANTISEPTIC, WITH OBSERVATIONS ON RAPID DEVELOPMENT OF RESISTANCE OF *E COLI* TO STREPTOMYCIN*

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THE ACTIVITY OF STREPTOMYCIN against gram negative organisms and its negligible absorption from the alimentary tract, as shown in the writings of Waksman and others,^{1, 2, 3, 4 5} has prompted the oral administration of this antibiotic in an attempt to reduce the bacterial flora in the large bowel preparatory to surgery. It is the purpose of this paper to present an appraisal of the effectiveness of oral streptomycin in reducing the numbers of intestinal bacteria in preoperative cases, in the light of the experiences of this clinic and a review of the publications from other clinics.

Preliminary reports of the effectiveness of streptomycin in intestinal prophylaxis by Zintel⁶ were encouraging. In a series of 15 patients who were given 0.25 Gm of streptomycin by mouth every six hours and followed with quantitative stool cultures, Zintel reported a marked and sustained reduction in the numbers of the three groups of organisms studied (coliform group, *streptococcus fecalis*, and clostridia). The patients in Zintel's series were followed from six to ten days after institution of streptomycin. A later paper⁷ reported essentially the same findings in greater detail.

Rowe, *et al*,⁸ studied the effects of oral streptomycin and sulfathaladine, singly and in combination, on the coliform group of organisms. These authors gave one group of patients oral streptomycin alone, a second group sulfathaladine, and a third group a combination of the two drugs. The dosage of streptomycin used was 2 Gm daily. A marked reduction in the numbers of coliform organisms in most of the patients in this series was found to occur within 48 hours, but a reversion was noted in two patients following prolonged administration. These authors concluded that streptomycin should not be used longer than 72 hours preceding surgery.

Poth⁹ suggested that streptomycin given orally before surgery might produce deleterious effects by virtue of the marked reduction in the bacterial flora, particularly in the upper alimentary tract, thereby interfering with the absorption of certain fat soluble substances, most important being vitamin K, resulting in an elevated prothrombin time. Another valid objection offered by this author was that in view of the rapid resistance to streptomycin developed by the intestinal bacteria, one would be reducing the usefulness of the drug in the treatment of postoperative complications, should such develop.

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The observations of Paine and Finland¹⁰ on streptomycin resistant and dependent bacteria are pertinent in this connection. While our work was in progress these authors reported work along similar lines with various groups of organisms, including *E. Coli*. They report that strains of streptomycin-sensitive, streptomycin-resistant, and even streptomycin-dependent organisms appear after exposure to various concentrations of streptomycin.

A series of 24 cases receiving oral streptomycin alone and nine cases receiving streptomycin and sulfathaladine in combination have been studied with quantitative estimations being made of the changes in stool bacteria which occur during preoperative administration of these drugs. The cases reported were selected at random from among patients admitted to Presbyterian Hospital for large bowel lesions, the diagnoses included carcinoma of the rectum, carcinoma of the sigmoid, chronic ulcerative colitis, diverticulitis, polyposis, and fistula in ano (tuberculous and non tuberculous). In this series, the three major groups of alimentary tract organisms were studied, namely the coliform group, the intestinal streptococci, and the clostridia, by the method described below.

BACTERIOLOGIC TECHNIC

Stools were obtained for culture before and every one or two days after the institution of oral streptomycin. The cases were followed for periods ranging from five to 14 days after the institution of chemotherapy. An emulsion of 1 Gm. of fresh wet stool in 9 cc. of sterile broth was prepared in a glass plunger type homogenizer. This 1:10 dilution of the stool was then carried through a continued series of eight 1:10 dilutions so that the last was $10^{-8}/x$ the concentration of the original stool specimen. One-half cubic centimeter portions of tubes two, four, six and eight were used for inoculating agar plates of the following media:

(1) Eosin methylene blue for coliform organisms. Surface lactose-fermenting colonies were counted after 24 hours incubation at 37° C.

(2) Modified Wilson Blair for clostridia. Two-tenths cubic centimeter of 8 per cent Ferric Chloride and 20 cc. of 20 per cent sodium sulfite were added just before use to 20 cc. of liquid meat infusion agar. Pour plates were made, the colonies of clostridia appearing as black spots in the medium after 24 hours anaerobic incubation.

(3) Two per cent Dextrose meat infusion agar, buffered with NaOH to pH 9.3 for streptococci. Pour plates were also made with this medium, the streptococci appearing as small millet seed shaped colonies in the medium, and colonies were counted after 72 hours incubation.

Colony counts were then made on the plate of highest dilution in which colonies appeared for each of the three groups of organisms. By this method a relatively accurate approximation of the total number of organisms in each stool was gained.

RESULTS AND INTERPRETATION

A total of 24 patients received oral streptomycin alone. 19 of whom received

resistance by *E Coli* in a group of ten cases chosen at random from this series

Preliminary titrations had shown that in these patients the *E Coli* isolated before administration of oral streptomycin were sensitive to and completely inhibited by 125 units of streptomycin per cubic centimeter After treatment the organisms rapidly became resistant to at least 100 units/cc Therefore a wide range was selected, *i e* 0 to 10,000 units/cc , distributed as in Figure 1

STREPTOMYCIN RESISTANCE OF E. COLI

UNITS/C C		0	19	39	78	156	312	625	1250	2500	5000	10000
LO	0	+	0	0	0	0	0	0	0	0	0	0
	2	+	+	+	+	+	+	0	0	+	+	+
	4	+	+	+	+	+	+	0	0	+	+	+
CO	0	+	0	0	0	0	0	0	0	0	0	0
	2	+	+	+	+	+	+	0	0	+	+	+
	4	+	+	+	+	+	+	0	0	+	+	+
B0.	0	+	0	0	0	0	0	0	0	0	0	0
	2	+	+	+	+	+	+	0	0	+	+	+
	4	+	+	+	+	+	+	0	0	+	+	+
O'D.	0	+	0	0	0	0	0	0	0	0	0	0
	2	+	+	+	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+	+	+	+
EP	0	+	0	0	0	0	0	0	0	0	0	0
	5	+	+	+	+	+	+	0	0	+	+	+
	6	+	+	+	+	+	+	0	0	+	+	+
TR.	0	+	0	0	0	0	0	0	0	0	0	0
	5	+	0	0	0	0	0	0	0	0	0	0
	6	+	+	+	+	+	+	+	+	+	+	+
BR	0	+	0	0	0	0	0	0	0	0	0	0
	4	+	+	+	+	+	+	0	0	+	+	+
CR	0	+	+	+	+	+	0	0	0	+	+	+
	2	+	+	+	+	+	0	0	0	+	+	+
	4	+	+	+	+	+	+	+	+	+	+	+
RI.	0	+	0	0	0	0	0	0	0	0	0	0
	8	+	+	+	+	+	+	0	0	+	+	+
PU	0	+	0	0	0	0	0	0	0	0	0	0
	2	+	+	+	+	+	+	0	0	+	+	+
	4	+	+	+	+	+	+	0	0	+	+	+
	6	+	+	+	+	+	+	0	0	+	+	+
	8	+	+	+	+	+	+	0	0	+	+	+

+ INDICATES GROWTH AT GIVEN STREPTOMYCIN CONCENTRATION
0,2,4 INDICATES DAY OF THERAPY WHEN CULTURE WAS OBTAINED

FIG 1

From each stool specimen the *E Coli* were isolated in pure culture on EMB agar An inoculum for titration was prepared by placing one loop of the organism into five cubic centimeters of streptomycin broth (a standard specified by the USFDA) and incubated at 37° C for five hours One drop of this inoculum was added to two cubic centimeters of the titration broth and incubated for 72 hours at 37° C and read at the end of that time for visible turbidity

The results revealed that prior to treatment the *E Coli* were inhibited in all but one case by the lowest concentration of streptomycin used, *i e* , 19

units/cc This one exception was resistant to 156 units/cc After 48 hours of oral streptomycin, the organisms isolated were found to be resistant to at least 156 units/cc in all but one case, this strain requiring six days for the development of resistance In one case the organism grew in all the titration concentrations after 48 hours of oral streptomycin This was observed on prolonged treatment in two other cases

A marked prozone phenomenon was observed in these titrations In the 2500 units/cc concentration and up flocculation was produced which obscured the gross reading by turbidity, so that growth was confirmed by plating on EMB agar After 48 hours of treatment with oral streptomycin the high streptomycin concentration tubes were found to contain heavy growth The zone of inhibition, between 156 units/cc and 2500 units/cc, was also confirmed since plating on EMB agar produced no growth or scant growth

These observations indicate that resistant strains of *E. Coli* develop with great rapidity within 48 hours after institution of streptomycin

The fact that *E. Coli* may be inhibited by concentrations of streptomycin below 2500 units/cc and yet not be killed by concentrations between 2500 units/cc and 10,000 units/cc is a phenomenon of considerable interest, and calls attention to a related phenomenon described by Eagle,¹¹ who observed a similar zone effect with penicillin

STOOL ASSAY FOR STREPTOMYCIN CONTENT

The stools of three patients who were given 4 Gm of streptomycin daily divided 1 Gm every six hours were assayed for streptomycin content It was found that within 48 hours after the initiation of therapy a level of 4,800 to 9,600 units of streptomycin per gram of wet stool was reached One patient was found to have 19,200 units/gram after six days of oral streptomycin It will be noted that these concentrations are greater than the prozone levels observed in the titrations, and are in the range where streptomycin resistant organisms proliferate

ORAL STREPTOMYCIN COMBINED WITH SULFATHALADINE

Because of the unreliable results obtained with oral streptomycin alone a series of preoperative patients were given oral streptomycin in combination with sulfathaladine, and daily colony counts of the stools by the method previously described were carried out Dosages given were 0.25 Gm of streptomycin and 1 Gm sulfathaladine every six hours by mouth Though this series is too small to permit valid conclusions the data on the nine cases so treated are here reported, since they appear to show results essentially similar to the response obtained with oral streptomycin alone (See Table III) It will be noted that only four of the nine cases showed a significant drop in the numbers of coliform and streptococcus colonies

In all four of these cases the effect was short-lived, the maximum reduction in the bacterial flora occurring within 48 to 72 hours after the institution

of treatment, and thereafter returning very rapidly to the pretreatment level, this level becoming re-established within five days after the institution of chemotherapy and within two days after the maximum drop. Only one of the nine cases showed a significant drop in the number of clostridia colonies, and this was temporary. All nine patients were followed at least four days, the longest being nine days. No toxic effects were observed in this series of cases.

TABLE III—*Response of Colony Counts to 10 Gm Streptomycin and 40 Gm Sulfathaladine Per Day*

Degree of Response	Number Giving No Response	Number Giving Temporary Response		Number Giving Prolonged Response		Total Number of Cases
		To 0.01%	To 0.001% or Less	To 0.01%	To 0.001% or Less	
<i>E. Coli</i>	5	1	3	0	0	9
Streptococci	5	4	0	0	0	9
<i>Cl. welchii</i>	8	1	0	0	0	9

CONCLUSIONS

A comparison of the results reported in this paper with previous publications has led us to the conclusion that oral streptomycin cannot be recommended for the preoperative preparation of patients requiring large bowel surgery, for the following reasons:

- (1) Reduction in intestinal flora is unpredictable and unreliable.
- (2) In a significant proportion of the cases which show a favorable early response to oral streptomycin, the organisms rapidly develop resistance to the drug.

Although our series of cases is too small to permit final conclusions to be drawn, it would seem that the probable development of resistance to streptomycin by the intestinal organisms would be likely to render the parenteral use of this drug ineffective should the patient develop postoperative complications which might ordinarily be treated with this drug. In view of these observations we feel that it would be wiser to reserve the use of streptomycin for the treatment of complications should they develop rather than to expend the drug effect in the preoperative preparation of the patient.

SUMMARY

1. A review of publications on the use of oral streptomycin in preoperative preparation of surgical cases is presented. The conflicting nature of those reports is emphasized.

2. A series of 24 cases treated at the Presbyterian Hospital with oral streptomycin is presented, together with the methods used to obtain serial quantita-

tion colony counts on the three groups of organisms studied, the coliform group, the streptococcus, and the clostridia

3 Results obtained were inconsistent. Approximately half of the cases treated showed no response in the coliform group to oral streptomycin, and of the cases showing a response, 50 per cent or $\frac{1}{4}$ of the total number of cases, showed a prolonged significant response.

4 Eighty-seven and seven-tenths per cent of the cases showed no significant reduction in the number of streptococci present in the stool.

5 Thirty-eight and nine-tenths per cent of the cases showed no significant reduction in the number of clostridia present in the stool.

6 Sensitivity titrations on the *E. Coli* group showed rapid development of resistance to streptomycin, and brought out the fact that many strains of *E. Coli* become able to proliferate in the concentrations of streptomycin which exist in feces.

7 A series of nine cases treated with combined streptomycin and sulfathaladine is presented. The results in this group are also inconsistent.

8 The authors conclude that oral streptomycin is unpredictable and unreliable, and its use in the preoperative preparation of surgical cases is not to be recommended.

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THE IMPORTANCE OF THE LEVEL OF THE LESION IN THE PROGNOSIS AND TREATMENT OF CARCINOMA OF THE RECTUM AND LOW SIGMOID COLON*

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IT IS NO LONGER POSSIBLE to be complacent about the adequacy of combined abdominoperineal resection, done in the classic fashion, in the treatment of carcinoma of the rectum and lower part of the sigmoid colon. This procedure, the result of the careful studies and the experience of Miles, unquestionably represents a logical and important advance in surgical management of malignant disease. However, it, in common with all operations, is constantly challenged by changing concepts, new information and advances in surgical technic.

It has been the practice of many surgeons to employ the operation of combined abdominoperineal resection in the treatment of all lesions of the rectum, and in those lesions of the sigmoid colon located so low that an exteriorization operation of some type is not possible. This concept of treatment has been questioned in recent years on two general scores. On the one hand, in cases in which there are lesions of the upper part of the rectum, the rectosigmoid and the lower part of the sigmoid colon, it has been proposed^{1, 8, 20, 22, 24} that operations as curative as combined abdominoperineal resection can be done which will at the same time conserve sphincteric function to some degree at least, secondly, it has been questioned whether the usual Miles operation is as curative for low-lying rectal and anal lesions as a more radical posterior excision.⁹

That the life and comfort of patients suffering from carcinoma of the terminal portions of the colon depend on an accurate answer to these questions is obvious. There can be no challenge to the contention that in carcinoma of the rectum and sigmoid colon, the operation which is proved to be the most efficacious in effecting cure should be done, regardless of whether or not a permanent abdominal colonic stoma is necessary. This assumes of course that differences in operative mortality rates in good risk patients are negligible, which we believe to be true. However, it would seem equally obvious that two procedures which are equally curative but in one of which preservation of the function of the anal sphincter is possible and in the other of which a permanent abdominal colonic stoma must be made are not of equal merit. An

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accurate appraisal of this situation demands an unbiased analysis of the factors involved

The determination of truly comparable survival rates in patients undergoing combined abdominoperineal resection, and in those undergoing the other procedures which have arisen to challenge it, is not as simple as might appear. It is well known that operability rates, resection rates and hospital mortality rates must be known for each procedure to be considered and must be carefully controlled. More important, and perhaps less well appreciated, is that there are many factors inherent in the growth itself which should be analyzed and understood with relation to such comparisons of the various operative procedures.

These factors, in addition to being important in the use of comparative statistical data, are important in considering the adoption of a relatively new and as yet unproved operative procedure. Obviously, it is not as yet possible to compare accurately the results from combined abdominoperineal resection, posterior resection, the Hochenegg pull-through procedure, perineal resection with primary anastomosis, anterior resection with primary anastomosis and the other procedures which have been employed for lesions in this region. Until such comparisons are possible, the surgeon should understand as thoroughly as possible the behavior of the growths in question and the factors affecting their prognosis. In this way, he may select a procedure which, though as yet unproved, is based on sound reasoning.

The histologic grade (Broders) of the lesion and the extent of the lesion as represented by its type (Dukes)¹¹ are two outstanding factors which must be studied and understood in any series of rectal and low sigmoidal carcinomas. It would seem that the location of the lesion, with respect to its distance from the anal margin, might also be a factor of some importance. Obviously, in comparing the survival rates of patients treated by anterior resection with those of patients treated by combined abdominoperineal resection, one should know, among other things, whether there is any difference in the prognosis of low-lying rectal lesions and of low sigmoidal lesions, when both are treated by combined abdominoperineal resection. If the low sigmoidal lesions have a significantly better prognosis than the low-lying rectal lesions when both are treated by the same operative procedure, then one must of course compare the survival rates after anterior resection, with restoration of intestinal continuity, *not* with those of all patients treated by abdominoperineal resection, but with those of patients having lesions at the same level of the bowel as the patients treated by anterior resection. Furthermore, if it were shown that patients having low-lying rectal lesions treated by combined abdominoperineal resection fare less well than those having lesions in the middle and upper parts of the rectum, it might be an impetus to the trial of a more radical removal of the very low-lying lesions.

It was because of these implications that a study was made of the effect of the level of the lesion on the prognosis in carcinoma of the rectum and the lower part of the sigmoid colon.

REVIEW OF THE LITERATURE

A careful review of the literature has failed to reveal a factual analysis allowing accurate conclusions as to the effect of the level of the lesion in the bowel on prognosis after surgical resection of the growth in cases of carcinoma of the rectum or sigmoid colon. There have been opinions expressed concerning this matter, however, some of which have of course been conflicting.

Lockhart-Mummery, in 1926, stated that patients having adenocarcinomas of the rectosigmoidal junction had a poorer prognosis than those having lesions in the rectum itself, he felt that one reason for this was the greater difficulty associated with removal of the regions of direct spread and nodal involvement in rectosigmoidal lesions. Coffey, in 1931, again expressed the opinion that patients having rectosigmoidal lesions are more difficult to cure than those having the lower-lying rectal lesions.

Dukes has carefully and accurately studied many phases of the pathology of rectal and sigmoidal cancers, but there are not available in his published work data as to the effect of the level of the lesion itself on the curability of the lesion. He stated¹² that he had concluded that in cases without involvement of lymph nodes the five year survival rates are the same regardless of location. However, he stated that in lesions with nodal involvement the results "varied to some extent with the position in the rectum of the malignant growth." It was his opinion that lesions in the midrectal region did less well than those in a similar stage of development located in the upper or lower part of the rectum. He felt that this was due to the more pronounced tendency for lateral spread in lesions in the midrectum.

Gilchrist and David,^{14, 15} in two recent publications, set forth some results of their careful studies of carcinoma of the bowel, which indicate that in their cases the low-lying lesions entailed a poorer prognosis than the higher-lying ones. They called the low-lying group the "extraperitoneal group." Since it has been shown in a previous study¹⁸ that the location of the growth with reference to the level of the peritoneal reflection has no effect on prognosis, other factors being equal, it may well be that the poorer prognosis in the "extraperitoneal group" of Gilchrist and David is due to their low location in the rectum, rather than to their being beneath the peritoneal reflection.

Barbosa, Waugh and Dockerty studied 105 cases of low rectal and anal adenocarcinomas and concluded from their study that the prognosis in these cases is poorer than in higher-lying rectal lesions.

Thus there is considerable suggestion in the recent literature that there is some relation between the level of the lesion and the prognosis. What data are available tend to support the idea that the lower-lying lesions have in general, a poorer prognosis than the higher-lying ones.

MATERIALS AND METHODS OF STUDY

From the files of the Mayo Clinic were selected the records of all patients

who, in the ten year period from 1931 through 1940, had undergone combined abdominoperineal resection for adenocarcinoma of the rectum and sigmoid colon and who had survived operation. All cases with metastatic growths in the liver or other distant sites, and thus in which the resection was purely palliative, were eliminated. The records of 453 patients were thus obtained. On careful review of the record of each patient, it was found that 65 cases were not suitable for inclusion in this study. A few had been incorrectly filed, and were in fact palliative resections, a few had had only the first stage of a two-stage combined abdominoperineal resection and for some reason had failed to have the second stage. Most of these 65 were not suitable for inclusion in this study because no accurate data were available as to the level of the lesion within the bowel. It should be stated that nearly all these cases with data insufficient to judge accurately the level of the lesion occurred in the first few years of the study, at a time when proctoscopic estimation of the level of the lesion was not routinely performed.

Three hundred and eighty-eight cases remained for study. Data were available in each case, from proctoscopic examination, digital examination of the rectum, from the surgeon's note and from the pathologic examination, as to the approximate level of the lesion. In general, the data from these various sources agreed. However, the data from proctologic examination were usually most clearly stated, since it has been the policy in the clinic for some time to report lesions as beginning a given number of centimeters above the anal margin. Because of this, and because clinically this proctoscopic estimation of the level of the lesion is of value in the planning of the surgical procedure, the distance from the anal margin as estimated by the proctoscopist has been used in classifying these lesions.

It is to be noted that the lesions thus are classified according to the distance from the anal margin to the lower edge of the lesion. It is freely acknowledged that this is not a really precise method of locating the lesions, but it has two advantages over a seemingly more precise method, namely the measurement of this distance in formalin-preserved surgical specimens. In the first place, as noted previously, it is the most important preoperative method of estimating the level of the lesion. Secondly, there is considerable shrinkage in preserved specimens and thus an accurate idea of the level of the lesion *in vivo* may not be obtained from a study of them.

Note was made in each case of the histologic grade of the lesion and of the presence or absence of nodal involvement, as reported by the pathologist examining the surgical specimen. The follow up correspondence was carefully reviewed to determine the survival or death of each patient in the series. Analysis by the direct method was then made of the five-year survival rates of patients having lesions at various levels in the bowel.

RESULTS

The results of this study are presented in a series of tables, which are in the main self-explanatory. These data allow the formation of certain con-

clusions as regards the effect of the level of the lesion on survival rates after combined abdominoperineal resection

It appears (Table I) that those patients whose lesions lie within approximately 5 cm of the anal margin have a poorer prognosis than those whose lesions lie above this level, both groups being treated by combined abdominoperineal resection. Those patients having lesions approximately 11 cm or more above the anal margin have a prognosis which is slightly better than that of the over-all group but in cases with nodal involvement these persons with high-lying lesions would seem to have a definitely better prognosis than those with either low-lying lesions or with lesions the lower edge of which ranges from 6 to 10 cm from the anal margin

TABLE I—*Survival Rates of Patients Having Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients*
0-5 cm	All cases	100	93	43	46.2
	Without	56	50	33	66.0
	With	44	43	10	23.3
6-10 cm	All cases	201	182	93	51.1
	Without	105	94	71	75.5
	With	96	88	22	25.0
11 cm or more	All cases	87	80	43	53.8
	Without	54	47	32	68.1
	With	33	33	11	33.3

* In this and all subsequent tables inquiry was as of January 1, 1946. All operations were performed in 1940 or earlier.

In order to obtain a more homogeneous group for analysis, the 248 cases in this series in which the lesions showed grade 2 (Broders) malignancy were analyzed in similar fashion (Table II). These data show the same general trend as those of the entire group, but the differences are more clear-cut. We believe that this group represents more accurately the true state of affairs, since the lesions are histologically similar through the group. It is again seen that patients whose lesions were within 5 cm of the anal margin had a poorer prognosis than those with lesions lying higher up and that those with lesions lying 6 to 10 cm removed from the anal margin had a poorer prognosis than those with lesions 11 cm or more removed from this point. Again, considering only lesions with nodal involvement, a location 11 cm or more removed from the anal margin allowed a much more favorable prognosis than did a lower location. In the group with grade 2 lesions without nodal involvement those patients with low-lying lesions again appear to have

CARCINOMA OF RECTUM

a prognosis less favorable than those with growths lying 6 cm or more above the anal margin

In order to obtain some further information on the critical levels, as regards prognosis, the data were again analyzed, this time breaking the cases down into groups at somewhat different levels (Table III)

TABLE II—*Survival Rates of Patients Having Grade 2 Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-5 cm	All cases	72	66	30	45.5
	Without	41	36	22	61.1
	With	31	30	8	26.7
6-10 cm	All cases	119	106	56	52.8
	Without	62	55	41	74.5
	With	57	51	15	29.4
11 cm or more	All cases	57	51	31	60.8
	Without	34	28	21	75.0
	With	23	23	10	43.5

TABLE III—*Survival Rates of Patients Having Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-2 cm	All cases	61	58	25	43.1
	Without	34	31	18	58.1
	With	27	27	7	25.9
3-6 cm	All cases	77	70	33	47.1
	Without	41	36	27	75.0
	With	36	34	6	17.6
7-10 cm	All cases	163	148	77	52.0
	Without	86	77	58	75.3
	With	77	71	19	26.8
11 cm or more	All cases	87	80	43	53.8
	Without	54	47	32	68.1
	With	33	33	11	33.3

This tabulation again serves to emphasize the relatively poor prognosis in patients with very low-lying rectal carcinomas. Thus, persons with lesions lying within 2 cm of the anal margin have, in the over-all group, a prognosis

which is less favorable than those with growths at any other level. In those with growths above this point, the prognosis gradually improves as the higher levels of the rectum are reached. It is interesting to note, in addition, that in cases with nodal involvement, the group with lesions lying 3 to 6 cm up from the anal margin had the poorest prognosis while those with lesions within 2 cm of the anal margin were only slightly better. The prognosis of lesions above 11 cm again was superior to that at any other level. Except for patients with lesions within 2 cm of the anal margin, in which instance the prognosis was poor, in lesions without nodal involvement there was not any significant improvement in prognosis as the higher levels were reached.

The data were similarly analyzed for grade 2 lesions only (Table IV). This more homogeneous group serves to substantiate the tendencies indicated by the over-all group thus analyzed.

TABLE IV—*Survival Rates of Patients Having Grade 2 Adenocarcinoma of the Rectum and Sigmoid Colon Treated by Combined Abdominoperineal Resection*

Level of Lower Edge of Lesion Above Anal Margin	Nodal Metastasis	Patients	Traced Patients	Lived 5 or More Years After Operation	
				Number	Per Cent of Traced Patients
0-2 cm	All cases	44	41	17	41.5
	Without	26	23	12	52.2
	With	18	18	5	27.8
3-6 cm	All cases	51	45	23	51.1
	Without	28	24	18	75.0
	With	23	21	5	23.8
7-10 cm	All cases	96	87	46	52.9
	Without	49	45	33	73.3
	With	47	42	13	31.0
11 cm or more	All cases	57	51	31	60.8
	Without	34	28	21	75.0
	With	23	23	10	43.5

COMMENT

It is apparent that patients with lesions lying very near the anal margin, treated by combined abdominoperineal resection, have a prognosis which is poorer than those with higher-lying lesions removed by the same operation. This unfavorable group probably embraces those patients having a lesion, the lower margin of which is within 5 or 6 cm of the anal margin, as estimated by proctoscopy. Patients with lesions, the lower margins of which are 6 or 7 to 10 cm removed from the anal margin, have a somewhat better prognosis, whether the growth is with or without nodal involvement, than patients with low-lying lesions, while those with lesions 11 cm or more from the anal margin have a prognosis superior to that of patients with lesions

lying below this level. These differences are not in every instance of great magnitude, but they do seem to indicate a consistent and definite difference in the behavior of lesions at varying levels in the bowel.

That such a difference occurs necessitates a consideration of two points. One of these is the possible basis for this difference in prognosis. The second is the application of a knowledge of these differences to the selection of operative procedures for carcinoma of the rectum and sigmoid, and to the interpretation of the results of these operations.

It is unlikely that there is any inherent variation in the malignancy of adenocarcinomas at varying levels of the bowel. Certainly there has not been demonstrated any tendency to higher grade lesions in growths located low in the rectum. Further, the differences in prognosis in this study were as significant, if not more so, when only grade 2 (Broders) lesions were considered as when the over-all group was analyzed. It has been suggested by some^{4, 24} that there is a slightly higher incidence of venous involvement and thus of visceral metastatic growths in the high-lying rectal lesions and low sigmoidal lesions than in the lower rectal lesions, although Dukes¹² stated that he found such involvement with equal frequency in all regions of the rectum and lower part of the sigmoid. If this slight difference does in fact exist, then the poorer prognosis of patients with low lesions occurs in spite of it, rather than because of it. It is doubtful indeed that differences in extent of invasion, as reflected in the typing of lesions after the method of Dukes, are responsible for differences in prognosis here, since these differences in prognosis are present when only cases with demonstrable nodal involvement are considered. It is further unlikely that the unfavorable tendencies of the low-lying lesions are due to their location beneath the peritoneal reflection, since it has been shown¹⁸ that the relation of growths to this reflection *per se* does not have any effect on prognosis.

The failure of combined abdominoperineal resection to effect as high a survival rate in patients with low-lying lesions may well, on the other hand, be due to its failure to cope with certain routes of lymphatic spread of the low-lying lesions. Without going into needless detail, it may be mentioned that there are, at least in theory and probably in fact, three routes of lymphatic spread in the lesions under consideration. These are of course, first, upward alongside the superior hemorrhoidal and inferior mesenteric vessels, second, laterally, along the lymphatic pathways accompanying the middle hemorrhoidal vessels and lying along the levator ani muscles, and third, inferiorly, along lymphatics destined eventually to accompany the inferior hemorrhoidal vessels and to drain in occasional instances to the superficial inguinal lymph nodes.

The differences in prognosis encountered in this study cannot be explained on the basis of differences in the efficacy of the operation in eradication of the upward spread in these lesions, for then one might expect the prognosis of the high lesions to be poorer than that of the low ones. Failure to excise adequately the inferior lymphatic spread of these lesions is not a probable explanation for several reasons. It has been demonstrated amply

by several careful studies^{6, 13 16 17} that spread along this inferior route is very uncommon in lesions of the upper part of the rectum and of the recto-sigmoid, and it has been recently emphasized by the careful studies of Dafoe that retrograde, or downward, lymphatic spread is likewise very unusual in the low-lying lesions of the rectum

However, it is possible that the differences in curability of the low-lying lesions, in contrast to those more removed from the anal margin, are due to spread along the lateral route, as has been suggested by others

Miles expressed the belief that lateral spread was the least important of the three possible lymphatic pathways. However, studies on lateral lymphatic spread in carcinoma of the rectum are by no means numerous or conclusive. One reason for this is that even with combined abdominoperineal resection only a relatively small amount of tissue lateral to the growth is removed, and thus only a small amount is available for study of spread in this direction. Most of the tissue of real interest in this mode of spread remains within the patient after operation. Dukes¹² as previously noted, expressed the opinion that lesions in the midrectal region did less well than similar growths in the lower or in the upper part of the rectum because of the tendency of the ampullary lesions to grow laterally along the lymphatics accompanying the middle hemorrhoidal vessels. Gilchrist and David¹³ noted, in their study of this problem, that 4 of 47 surgical specimens studied showed lateral nodal involvement along the superior surface of the levator ani muscle, these cases appeared to have lesions the lower margins of which were approximately 5 cm or more from the anal margin. In addition, in one of the two necropsy cases that they reported, in both of which the patients died a few days after combined abdominoperineal resection, there was a single involved node left behind, situated about 1 cm lateral to the point of severance of the levator ani muscle.

Coller, Kay and MacIntyre, who likewise made an extensive and thorough study of metastatic growths in lymph nodes in cases of carcinoma of the rectum, also noted good evidence of lateral lymphatic spread occurring in cases in which the superior route of spread was *not* blocked. Thus, in one of their necropsy cases, with a grade 2 carcinoma right at the anal margin, there were only seven nodes involved, all these being along the course of the right middle hemorrhoidal artery. Also, they pointed out that in seven of their 19 cases of very low-lying rectal cancers there was evidence of nodal involvement up to the margin of the excision of the levator ani muscle, which certainly must be construed as evidence of lateral spread. Further these were not cases showing choking of the upper lymphatics. They further noted that in no lesion in which the inferior border was 3 cm or more above the mucocutaneous junction (which would probably correspond to a level about 5 cm above the anal margin as estimated by proctoscopy) did they find metastatic growths along the lateral zone of spread.

Dafoe also has studied the lateral spread of carcinomas lying within 4.5 cm of the pectinate line, in a careful dissection of 100 specimens of such fai-

advanced cases. He again noted evidence in the removed specimens of lateral spread, but the presence of such spread in these far-advanced cases has somewhat less significance than in the less extensive cases studied by some other investigators.

In summary, it is nearly certain that lateral spread does occur occasionally in those far-advanced cases in which there is blockage of the superior zone of spread. It is further very probable, from the data recorded in the literature, that it also occurs fairly often in less extensive lesions the lower margins of which are within 5 or 6 cm. of the anal margin, as estimated by proctoscopic examination, and that in point of fact in such instances, it, along with the superior zone of spread, is a normal route of lymphatic metastasis and not an abnormal one taken only when the so-called normal routes are plugged with malignant deposits.

Such lateral spread beyond the line of resection carried out by the combined abdominoperineal operation is the probable explanation for the inferior prognosis in patients with lesions lying within 6 cm. of the anal margin. In lesions the lower margins of which were above this level, the lateral zone of spread was probably rarely involved, and thus failure to excise it completely in the resection did not lessen the chances for survival of the patient. It is not immediately apparent why patients with lesions the lower margins of which lay 3 to 6 cm. above the anal margin seemed to have a somewhat poorer prognosis than those with lesions in contiguity to the anus, when nodes are involved.

These matters have a very practical importance to the surgeon called on to treat malignant lesions of the rectum and sigmoid colon, for they influence to a great extent his choice of the surgical procedure for a given patient. As stated in the opening of this paper, this has become so since the classic combined abdominoperineal resection is now challenged in the treatment both of low-lying rectal lesions and of rectosigmoidal and sigmoidal lesions.

It is to be noted that the mere occurrence of a less favorable prognosis in patients with low-lying rectal lesions does not mean that it is possible to improve the prognosis in this group by more extensive surgical treatment.

Yet, it does become justifiable to inquire if a more radical removal of tissue in the region of lateral spread is possible in lesions within 5 or 6 cm. of the anal margin. Dixon⁹ has suggested that radical posterior resection, preceded by the formation of an abdominal colonic stoma and ligation of the superior hemorrhoidal vessels at a first stage, may in fact entail a more thorough removal of tissue in this region. A study of survival rates in a group of cases in which lesions the lower margins of which are within 5 or 6 cm. of the anal margin are treated by such a resection may help answer this problem, when compared to the survival rates in a similar group treated by the Miles operation.

Further, it has in recent years seemed proper to a number of surgeons to discard abdominoperineal resection for early or moderately advanced lesions the lower margins of which are 11 cm. or more removed from the anal margin, in favor of anterior resection with primary anastomosis^{8, 16, 25}. It is our opinion that this is justifiable, and indeed desirable, on the basis of the data previously

referred to concerning lymphatic spread of such lesions. The survival rates at present available confirm this conclusion.¹⁰

There remains a borderline zone, extending from 5 or 6 cm above the anal margin to 10 or 11 cm above this point. It is very difficult to effect an anastomosis safely after resection of a growth located in this region, yet the rarity of lateral and retrograde spread in such lesions strongly suggests that sacrifice of the perineum and anal sphincters is not necessary. Thus a combined abdominoperineal resection with preservation of the anal sphincters^{1, 23} has seemed to us to be the advisable procedure for growths located in this region. It should be emphasized, however, that the final decision as to whether this procedure, segmental resection with restoration of intestinal continuity, or the Miles operation is to be performed in a given case can be made only at the operative table after mobilization of the sigmoid, rectosigmoid and upper part of the rectum.

A final judgment as to the efficacy of this sphincter-conserving operation as well as to that of other operations employed for lesions in this region must depend on a carefully controlled comparison between the survival rates allowed by them and those procured by the classic combined abdominoperineal resection for lesions at comparable levels in the bowel.

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MALIGNANT TUMORS OF THE COLON AND RECTUM*

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MALIGNANT TUMORS OF THE COLON and rectum were found at Duke Hospital in 441 patients during the 15-year period 1931-1945. The incidence, symptomatology, treatment and results in this group have been analyzed and form the basis of this report.

INCIDENCE

Tabulation by site, sex, and color is shown in Table I, and by age in Table II. The frequency of these lesions as compared with the number of hospital admissions gradually increased until the last five years when the rate practically stabilized at one patient in every 337 admissions having a malignant tumor of the colon or rectum.

HISTORY

Twenty and four-tenths per cent of this group gave a family history of malignant tumor. The accuracy as to site was frequently questionable, but lesions most commonly occurred in the stomach, uterus and cervix, bowel, and skin in that order.

Operations performed before coming to Duke Hospital but after the onset of symptoms which ultimately led to the diagnosis of malignancy were: Colostomy 11, ileostomy two, resection of tumor five, exploratory laparotomy nine, appendectomy four, and biopsy of rectal lesion four. The infrequency of rectal biopsy is emphasized. Hemorrhoidectomy or repeated injections for hemorrhoids were carried out in 9 per cent of patients with lesions of the rectum or rectosigmoid. Most surgery for lesions proximal to the rectosigmoid had been emergency procedures, usually for intestinal obstruction.

The duration of symptoms, calculated from onset of first symptom to time of reporting to the hospital, averaged 8.7 months for the entire group, and varied from 6.3 months in the hepatic flexure group to 11.7 months for lesions of the splenic flexure. In three patients small lesions were found during operation for causes other than carcinoma and thus were diagnosed prior to the onset of symptoms. Much difficulty was encountered in determining the time of change from a benign lesion to malignancy in patients with polyposis. Table III shows the duration of symptoms in each group by economic status, race, service or private.

In the detailed consideration of symptoms, signs and accessory clinical data, the consolidation of the lesions into three groups instead of nine appeared justified because of the similarity of these findings. The cecum, ascending

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colon and hepatic flexure were grouped as the right colon, the transverse colon, splenic flexure, descending colon, and sigmoid as the left colon, and the recto-sigmoid and rectum considered as the third group

The symptoms in each group are shown in Tables IV, V, and VI, and in Table VII, the most frequent symptoms are compared. In two of the left colon

TABLE I*—*Site, Sex and Race of 441 Malignant Tumors of Colon and Rectum*

Site	Total		Male		Female		White		Colored	
	No	%	No	%	No	%	No	%	No	%
R	229	51.9	127	55	102	45	179	78	50	22
RS	29	6.6	18	62	11	38	27	93	2	7
S	63	14.3	35	55	28	45	53	84	10	16
DC	20	4.5	6	30	14	70	19	95	1	5
SF	8	1.8	7	87	1	13	6	75	2	25
TC	8	1.8	3	37	5	63	6	75	2	25
HF	17	3.9	10	59	7	41	15	88	2	12
AC	23	5.2	15	65	8	35	21	91	2	9
C	44	10.0	30	68	14	32	40	91	4	9
Total	441		251	57	190	43	366	83	75	17

*(In this and subsequent tables, all abbreviations for site of lesions are: R, rectum, RS, rectosigmoid, S, sigmoid, DC, descending colon, AC, ascending colon, SF, splenic flexure, TC, transverse colon, HP, hepatic flexure, C, cecum.)

TABLE II—*Distribution by Age*

	10-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
R	1	9	24	36	60	77	18	4
RS	0	2	3	6	8	7	3	0
S	0	3	4	12	20	18	6	0
DC	1	1	0	1	3	2	0	0
SF	0	1	2	3	5	6	2	1
TC	0	0	1	1	1	4	1	0
HF	0	2	2	7	2	2	2	0
AC	1	0	2	2	9	7	2	0
C	1	3	3	8	13	11	5	0
Total No	4	21	41	76	121	134	39	5
Total %	0.9	4.8	9.3	17.2	27.4	30.4	8.9	1.1

group and 13 of the rectum and rectosigmoid group, the first symptom was not clearly enough differentiated to permit inclusion. In 7 per cent of patients with lesions of the right colon and only 5 per cent of those of the left colon, intestinal obstruction came on rapidly in the absence of earlier symptoms. As would be expected, however, intestinal obstruction (as indicated by constipation, nausea, vomiting and distention) was more frequent with left colon lesions. Of the 84 patients with right colon lesions in this series, 23 per cent felt an abdominal mass, 29 per cent had marked weakness, and the remainder various gastro-intestinal complaints. Four (5 per cent) patients felt a mass and 12 (14 per cent) noted weakness, prior to the onset of other symptoms.

Changes in bowel habit and stool were frequent in all patients, but such symptoms predominated in the rectum and rectosigmoid group. Blood and mucus in the stool, constipation, diarrhea, and more localized symptoms such as tenesmus, decreased caliber of stool and rectal fullness occurred repeatedly. Symptoms of obstruction were not as common as in the left colon group. A not infrequent history was that of melena lasting only a day or two followed by an asymptomatic period of several months before characteristic symptoms appeared.

TABLE III—*Duration of Symptoms in Months Prior to Reporting to Hospital*

	R	RS	S	DC	SF	TC	HF	AC	C
Average	8.8	9.4	8.6	6.9	11.7	8.0	6.3	10.1	8.5
Service	9.6	10.3	9.6	6.1	10.4	4.0	6.3	10.8	7.1
Private	7.3	8.4	7.3	7.4	15.0	8.6	6.3	8.6	9.3

TABLE IV—*Symptoms in 84 Patients with Lesions of the Right Colon*
Number in parentheses indicates frequency as first symptom

Abdominal pain	62 (48)	Vomiting	17 (0)
Weakness	24 (12)	Constipation	15 (1)
Melena	23 (4)	Diarrhea	12 (6)
Nausea	20 (0)	Anorexia	11 (0)
Abdominal mass	19 (4)	Distention	7 (1)
Alternating diarrhea and constipation			2 (0)
Acute obstruction as first symptom			5

TABLE V—*Symptoms in 99 Patients with Lesions of the Left Colon*
Number in parentheses indicates frequency as first symptom

Abdominal pain	71 (33)	Alternating diarrhea and constipation	10 (4)
Melena	53 (10)	Abdominal mass	10 (3)
Constipation	42 (22)	Mucus in stool	10 (0)
Nausea	25 (0)	Tenesmus	8 (0)
Vomiting	23 (0)	Anorexia	4 (0)
Distention	22 (3)	Urinary	3 (0)
Diarrhea	20 (12)	Rectal fullness	2 (0)
Weakness	13 (3)	Aching rectal pain	1 (1)
Decreased caliber of stool	12 (1)		
Acute obstruction as first symptom			5

Although abdominal pain was the most frequent symptom in both colon groups, and fifth most common in the rectum and rectosigmoid group, no detailed analysis as to location, severity, character or radiation of the pain was made. Variation in these manifestations was dependent upon site of lesion, degree of obstruction, involvement of other organs, presence of infection, and probably other factors.

In 239 of the 441 records, the amount of weight loss was stated. The average for this group was 25.6 pounds. The average loss for 138 of the 258 patients with lesions of the rectum and rectosigmoid was 24.2 pounds, for 57 of the 99 left colon lesions 24.6 pounds, and for 45 of the 84 right colon lesions 31.5 pounds (Table VIII).

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EXAMINATION

The findings of principal interest on physical examination pertained to the abdomen, and Table IX summarizes the most frequent signs. Tenderness was usually found over the site of the lesion and was infrequently severe. The signs of peritoneal irritation occurred with complications such as obstruction or perforation. Distention was a fairly common finding and varied in severity depending on the degree of obstruction. There were 33 patients classified as

TABLE VI—*Symptoms in 258 Patients with Lesions of the Rectum and Rectosigmoid. Number in parentheses indicates frequency as first symptom.*

Melena	220 (80)	Aching rectal pain	20 (14)
Constipation	115 (62)	Inability to empty	15 (0)
Tenesmus	77 (10)	Urinary	14 (0)
Diarrhea	73 (40)	Distention	13 (0)
Abdominal pain	68 (18)	Alternating diarrhea and constipation	12 (4)
Mucus in stool	60 (3)	Anorexia	7 (0)
Decreased caliber stool	58 (3)	Nausea	7 (0)
Weakness	23 (6)	Vomiting	7 (0)
Rectal fullness	23 (5)	Abdominal mass	3 (0)

TABLE VII—*A Comparison of the Five Most Frequent Symptoms in Each Group*

Rectum and Rectosigmoid (258 Patients)		Left Colon (99 Patients)		Right Colon (84 Patients)	
Melena	220 (85%)	Abdominal pain	71 (72%)	Abdominal pain	62 (74%)
Constipation	115 (46%)	Melena	53 (53%)	Weakness	24 (29%)
Tenesmus	77 (30%)	Constipation	12 (42%)	Melena	23 (27%)
Diarrhea	73 (28%)	Nausea	25 (25%)	Nausea	20 (24%)
Abdominal pain	68 (26%)	Vomiting	23 (23%)	Abdominal mass	19 (23%)

TABLE VIII—*Weight Loss in Pounds*

	5-20	21-40	41-60	61-80	81-100
Rectum and rectosigmoid	72 (52 2%)	50 (36 4%)	9 (6 5%)	5 (3 6%)	2 (1 5%)
Left colon	32 (56 1%)	17 (29 9%)	4 (7 0%)	4 (7 0%)	0
Right colon	15 (33 4%)	19 (42 3%)	7 (15 5%)	2 (4 4%)	2 (4 4%)

completely obstructed who required immediate surgical intervention or, in a few instances, prolonged nonoperative treatment to relieve the obstruction. An abdominal mass was more often palpable in lesions of the right colon than elsewhere.

Of 229 cases of rectal malignancy, the lesion was felt by digital examination in 222, not felt but seen by proctoscopy in five, and no examination was recorded in two. Details regarding the lesion were recorded with variable accuracy. The mass was described as movable in 36 and fixed in 54. In position, it was on the right in eight, left in 13, anterior in 26, posterior in 23, and encircled the rectum in 64.

Complicating and intercurrent diseases were found as follows: Hypertensive vascular disease 82, cardiac disease with decreased reserve 24, obesity 20,

diabetes three, pulmonary tuberculosis one, bronchiectasis one, hyperthyroidism one, chronic alcoholism one, and senile dementia one. Generalized arteriosclerosis, benign prostatic hypertrophy, secondary anemia, and similar diagnoses were not tabulated.

The extent of the laboratory examinations depended on the indications, but all patients had at least hemoglobin, white blood cell count, blood serology, and

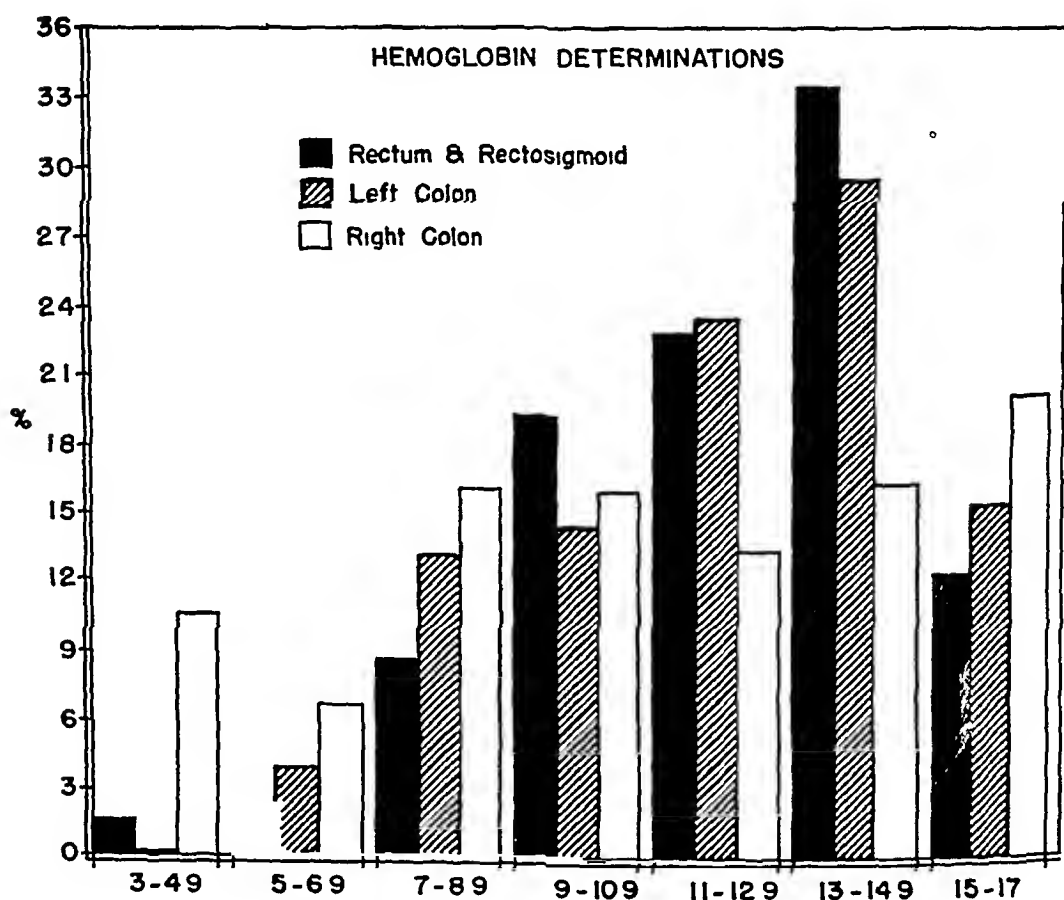


FIG 1—Hemoglobin determinations

urinalysis. The hemoglobin determinations (Sahli) are shown in Figure 1. The anemia was more severe in lesions of the right colon. The percentage of patients who had less than 90 Gm. of hemoglobin was 13 per cent for rectum and rectosigmoid, 17 per cent for left colon, and 34 per cent for right colon. Stool examination for occult blood was nearly always positive when done. Of 212 patients who had lesions of the rectosigmoid or colon, the stool was positive for occult blood in 78 of the 92 examined.

The radiologic findings were positive by barium enema in 81 per cent of right colon lesions and 88 per cent of left colon lesions. Of the 99 patients with right colon lesions 37 showed some degree of obstruction and 44 an irregularity or other alteration which was either diagnostic or highly suggestive of malignancy.

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nancy Of the 84 lesions of the left colon, 21 showed some degree of obstruction and 53 an irregularity The majority of the remaining patients did not have barium enema visualization of the colon, usually because of complete obstruction or obvious diagnosis In non-obstructing lesions of the rectum and rectosigmoid, barium enema was given to rule out a second lesion in the colon

TABLE IX—*Examination of Abdomen, Positive Findings*

	Rectum and Rectosigmoid	Left Colon	Right Colon
Tenderness	31 (12%)	26 (26%)	18 (21%)
Distention	34 (13%)	28 (28%)	13 (15%)
Palpable masses	17 (7%)	35 (35%)	58 (69%)

TABLE X—*Operative Procedures in 316 Patients*

	R	RS	S	DC	SF	TC	HF	AC	C
Palliative									
Colostomy	53	5	14	1	2				
Ileostomy									1
By-pass				1	1	2	2		8
Resection	2	1	5	1				1	
Exploration only	6	3	3	4		1	1	1	7
Preliminary									
Colostomy	8	2	7	3	1				
Cecostomy			1	4					
Definitive									
Resection and anastomosis	1	3	13	6	4	2	10	10	20
Exteriorization		2	15	5	1	3			
Combined resection	72	6	2	1					
Miscellaneous	5	1	1						

TABLE XI—*Resectability in 441 Patients, Determined by Percentage of Total Patients, Patients Admitted and Patients Operated Upon*

	R	RS	S	DC	SF	TC	HF	AC	C	-
Total patients	34 1	41 4	49 2	60 0	62 5	62 5	58 8	43 5	45 5	
Patients admitted	40 4	42 9	50 8	60 0	62 5	62 5	58 8	45 5	48 8	
Patients operated	54 5	54 5	56 4	63 1	62 5	62 5	76 8	83 3	55 5	

COURSE OF PATIENTS

Three hundred and ninety-eight of the 441 patients were admitted to the hospital Of the 43 patients not admitted, 16 elected to go elsewhere for treatment, ten refused admission, eight asked for deferred admission but did not return, and two came for irradiation therapy only Seven patients were obviously inoperable and were sent home for terminal care

Three hundred and sixteen of the 398 patients who were admitted had a total of 335 major operations (closure of colostomy not included) The course of the 82 patients not operated upon was as follows Twenty-six patients were inoperable and were discharged (colostomy not indicated), and ten were inoperable and died in the hospital The two most frequent causes of inoperability were a fixed lesion with frozen pelvis and a large nodular liver

Operation was not performed in six patients because of severe cardiovascular disease. Thirty-three patients refused operation and four patients were given irradiation only. Three patients thought to be operable died prior to operation, two of urinary tract infection (not due to obstruction by tumor), and one of peritonitis following perforation of the malignancy.

PREOPERATIVE CARE

The most important factors determining preoperative procedures were (1) degree of obstruction, (2) alterations of nutrition and chemical balance,

TABLE XII—*Lymph Node Metastases in Resected Lesions. The questionable nodes were those not mentioned in the pathologic report, or not available for study as in the limited rectal tumor resections.*

	R	RS	S	DC	SF	TC	HF	AC	C
Nodes positive	23	4	8	2	1	0	1	3	6
Nodes negative	28	5	13	5	3	4	4	3	8
Nodes questionable	27	3	10	5	1	1	5	4	6

TABLE XIII—*Postoperative Deaths Which Followed Exploration or Palliative Procedure*

No	Year	Site	Age Sex	Operation	Cause	P O Day Autopsy
1	1939	R	66 M	Colostomy	Peritonitis	20 No
2	1940	R	22-M	Colostomy	Shock and infection	3 No
3	1941	R	83-F	Colostomy	Widespread metastases	6 Yes
4	1942	R	73 M	Colostomy	Cardiac failure	19 No
5	1943	R	68-F	Colostomy	Pulmonary embolus	8 No
6	1943	R	40 F	Exploration	Peritonitis	2 Yes
7	1944	R	60-M	Colostomy	Cerebral vascular accident	12 No
8	1937	RS	50 F	Cecostomy	Obstruction and chem imbal	26 No
9	1937	RS	65-M	Combined Resection	Peritonitis	10 No
10	1935	S	42-M	Resection	Pneumonia	8 No
11	1942	S	40-F	Exploration	Hepato-Renal syndrome	32 No
12	1938	DC	42-M	Resection	Peritonitis	17 Yes
13	1941	DC	71-M	Exploration	Pneumonia	10 No
14	1944	DC	67-F	Exploration	Obstruction	50 No
15	1934	TC	66-M	Ileocolostomy	Pneumonia	2 No
16	1940	HF	43 M	Ileocolostomy	Peritonitis	9 Yes
17	1934	C	23 M	Ileocolostomy	Peritonitis	37 Yes
18	1936	C	47-M	Ileocolostomy	Peritonitis	17 No
19	1939	C	61-M	Ileocolostomy	Widespread metastases	14 Yes
20	1943	C	38 F	Exploration	Shock and hemorrhage	1 Yes

and (3) concurrent disease. The treatment of the intestinal obstruction depended on its severity. Whereas most patients on a low residue intake were adequately decompressed by repeated enemas with or without the aid of a Miller-Abbott tube, some required a cecostomy or colostomy. The attainment and maintenance of an empty bowel both preoperatively and postoperatively was considered the most important single factor in the recovery of these patients. A sulfonamide, usually sulfasuxidine, was routinely employed for several days before operation and penicillin was administered for 48 hours preoperatively after these preparations were available. Streptomycin was not

TUMORS OF COLON AND RECTUM

given to any patient in the group under consideration. Alterations in fluid and electrolyte balance, hypoproteinemia, vitamin deficiency, and anemia were ascertained by history, physical and laboratory findings, and corrected by appropriate measures.

TABLE XIV—*Postoperative Deaths Following Preliminary Colostomy for Obstruction*

No	Year	Site	Age Sex	Operation	Cause	P O Day Autopsy
1	1936	R	39-M	Colostomy	Peritonitis	12 No
2	1938	R	48-M	Colostomy	Peritonitis	8 No
3	1940	R	62-F	Colostomy	Peritonitis	3 No
4	1942	R	52-M	Colostomy	Uremia	4 No
5	1932	RS	25-M	Colostomy	Pneumonia	10 No
6	1941	S	55-F	Colostomy	Peritonitis	4 Yes
7	1944	S	73-F	Colostomy	Pulmonary embolus	11 No
8	1944	DC	80-F	Colostomy	Cardiac failure	8 No

TABLE XV—*Postoperative Deaths Following Resections. Operations abbreviated as follows: Abd-per—combined abdominoperineal resection, Obs-res—obstructive resection, Res-ana—resection and primary anastomosis, and Rt-col—right colon resection with ileotransverse colostomy.*

No	Year	Site	Age Sex	Operation	Cause	P O Day Autopsy
1	1933	R	62-F	Abd-per	Peritonitis	14 No
2	1937	R	58-M	Abd-per	Peritonitis	6 Yes
3	1937	R	68-M	Abd-per	Pneumonia	11 No
4	1941	R	53-M	Abd-per	Pulmonary embolus	5 Yes
5	1941	R	50-M	Abd-per	Peritonitis	12 No
6	1942	R	68-M	Abd-per	Uremia	4 No
7	1943	R	54-F	Abd-per	Pulmonary embolus	1 No
8	1943	R	70-M	Abd-per	Cerebral vascular accident	3 Yes
9	1943	R	64-M	Abd-per	Cardiac failure	4 No
10	1943	R	50-F	Abd-per	Hemorrhage and shock	3 No
11	1944	R	68-F	Abd-per	Cardiac failure	5 No
12	1944	R	60-M	Abd-per	Pneumonia	8 No
13	1934	RS	62-F	Abd-per	Cerebral vascular accident	2 No
14	1939	RS	52-M	Coffey	Peritonitis	3 Yes
15	1940	RS	75-M	Abd-per	Cerebral vascular accident	6 No
16	1933	S	55-F	Obs-res	Peritonitis	5 Yes
17	1934	S	63-F	Obs-res	Obstruction and chemical imbalance	11 Yes
18	1938	S	26-M	Obs-res	Pneumonia	6 No
19	1939	S	64-M	Obs-res	Pneumonia	10 Yes
20	1941	S	47-M	Obs-res	Peritonitis	11 Yes
21	1945	S	61-M	Obs-res	Peritonitis	11 No
22	1938	DC	65-M	Obs-res	Chemical imbalance	17 No
23	1944	DC	83-F	Res-ana	Cardiac failure	6 Yes
24	1934	SF	63-M	Res-ana	Peritonitis	8 Yes
25	1944	TC	71-F	Res-ana	Shock following plasma	5 No
26	1933	C	54-M	Rt-col	Pneumonia	11 No
27	1935	C	64-F	Rt-col	Hemorrhage and shock	1 No
28	1936	C	67-M	Rt-col	Peritonitis	9 No
29	1941	C	75-F	Rt-col	Pulmonary embolus	29 Yes

OPERATIONS

The various surgical procedures carried out are shown in Table X. Exploration alone and various palliative procedures were performed in 126 patients. The majority of these patients had a colostomy. Ileotransverse colostomy was

performed in 13, palliative resection in ten, and colocolostomy in one. Points of invasion and metastases either alone or in combination in these 126 patients were as follows: Invasion of pelvic or abdominal wall, 54, metastases to liver, 38, invasion of the urinary bladder, 31, peritoneal implants, 26, abdominal carcinomatosis, 14, periaortic lymph node enlargement, 11, and invasion of small bowel, 6. Although liver metastases or bladder invasion did not necessarily contraindicate resection, hope for cure could obviously not be held. Preliminary decompressing operations were performed in 26 patients, usually as an emergency procedure, prior to a later attempt to resect the lesion.

Operations which justified a reasonable hope for cure are shown in Table X under definitive procedures. The combined resections were the one-stage combined abdominoperineal resection (the Miles procedure). Of the miscel-

TABLE XVI—*Summary of Postoperative Mortality*

	Palliative Operations	Postoperative Deaths	Preliminary Operations	Postoperative Deaths	Resections	Deaths
R	61	7 (11%)	8	4 (50%)	78	12 (15%)
RS	9	2 (22%)	2	1 (50%)	12	3 (25%)
S	22	2 (9%)	8	2 (25%)	31	6 (19%)
DC	7	3 (43%)	7	1 (14%)	12	2 (17%)
SF	3	0	1	0	5	1 (20%)
TC	3	1 (33%)			5	1 (20%)
HF	3	1 (33%)			10	0
AC	2	0			10	0
C	16	4 (25%)			20	4 (20%)
Total	126	20 (15.9%)	25	8 (30.8%)	183	29 (15.8%)

TABLE XVII—*Postoperative Mortality During the Three Periods from 1931 to 1945*

	Palliative Operations	Mortality	Preliminary Operations	Mortality	Resections	Mortality
1931-35	21	14%	3	33%	22	32%
1936-40	50	16%	11	27%	51	16%
1941-45	55	16%	12	33%	110	13%

laneous procedures, two had local excision of rectal lesions as they refused more extensive resection. One had preliminary colostomy followed by resection and anastomosis through a posterior perineal approach. Two others had preliminary colostomy followed by perineal resection of the rectal lesion, and implantation of the distal loop into the vagina. One rectosigmoid lesion was removed by a modified Coffey procedure. One patient with polyposis and malignant change in the sigmoid had a resection from mid-transverse colon to lower sigmoid. The proximal loop was brought out as a colostomy and the distal loop turned in.

The resections for lesions of the hepatic flexure, ascending colon and cecum extended from the terminal ileum to transverse colon, continuity being re-established by ileotransverse colostomy. For lesions of the transverse colon, splenic flexure, descending colon and sigmoid, primary resection and anastomosis and

exteriorization procedures were employed in about the same number of patients. More recently, however, primary resection and anastomosis was usually performed. A closed two-layer anastomosis with silk was commonly employed. Open anastomosis was infrequently carried out.

In a number of patients, resection of adjacent structures was necessary because of tumor invasion. These included small bowel, stomach, abdominal wall, gallbladder, ureter, urinary bladder, vas deferens, uterus, tubes, and ovaries. Among the unusual operative findings, four cases merit comment. In three patients, two with sigmoid and one with cecal carcinomas, intussusception was present. The fourth patient had an adenocarcinoma of the cecum which had caused obstruction at the ileocecal valve. This had been partially relieved by a spontaneous ileocolic fistula.

TABLE XVIII—*The Results in 126 Palliative Operations. Average survival and survival range in months*

	Total Operations	Died in Hospital	Lost to Follow- up	Total Fol- lowed	Living	Dead	Average Survival	Survival Range
R	61	7	1	53	1	52	13	1-80
RS	9	2	0	7	1	6	11	2-33
S	22	2	1	19	1	18	7	2-25
DC	7	3	0	4	0	4	7	1-14
SF	3	0	0	3	0	3	6	1-15
TC	3	1	0	2	0	2	12	2-23
HF	3	1	0	2	0	2	5	3-7
AC	2	0	0	2	0	2	7	2-13
C	16	4	0	12	0	12	4	1-13

RESECTABILITY

In Table XI are shown the percentage of patients in whom the lesion was resected with reasonable hope of cure. Preliminary decompressing operations were omitted from the calculations. Resectability may be expressed as percentage of patients seen, of patients admitted to the hospital, or patients recommended for operation, or of patients subjected to operation, the latter being the most frequent form. It seems apparent that resectability expressed as percentage of resections among total patients seen would give the most comparable and accurate statistics, as this would probably represent the best index of the willingness and ability of the surgeon to extend help to the poorer risks. It might also indicate progress in early diagnosis of these lesions. By careful choice of patients, the other three expressions of resectability could be extended to high percentages, and reflect selectivity rather than resectability. For comparison, the table shows resectability computed as indicated.

Based upon the entire group, resectability was slightly higher in white than colored, and appreciably higher in the female than male. It was slightly greater in those under 60 years than those over this age.

Pathology. All the resected lesions and the inoperable tumors from which a biopsy was obtained were adenocarcinomas with four exceptions. One cecal and two rectal tumors were lymphosarcomas, and one cecal lesion was an

unclassified sarcoma. These will be considered separately in the follow-up studies. The lesions were not graded or classified. The importance of lymph node metastases is generally recognized. Unfortunately, in a substantial number of pathologic reports the presence or absence of lymph nodes was not mentioned (as noted in Table XII) thus detracting from the value of this phase of the analysis. Four squamous cell carcinomas of the anus were found during the study but were not included.

Postoperative Complications The non-fatal complications included 13 wound infections and two wound disruptions. Ten patients developed intestinal obstruction, three had peritonitis, and one postoperative hemorrhage. Thrombophlebitis occurred 11 times and pulmonary embolus twice. Seven patients had atelectasis or pneumonia. Cardiac failure and unexplained pleural effusion

TABLE XIX—*The Results in 183 Resections from 1931 to 1945 Inclusive, the Follow-up Period Closing April 1947. The living are survivors for 16 months to 17 years*

	Total Resections	Died in Hospital	Lost to Follow up	Total Followed	Dead	Living
R	78	12	3	63	24	39
RS	12	3	0	9	4	5
S	31	6	1	24	8	16
DC	12	2	1	9	4	5
SF	5	1	0	4	2	2
TC	5	1	0	4	3	1
HF	10	0	2	8	3	5
AC	10	0	0	10	5	5
C	20	4	1	15	5	10

TABLE XX—*The Five Year Survivals for Resections Performed 1931 Through 1940*

	Total Resections	Died in Hospital	5 Year Survivors		
			Living	Dead	%
R	26	3	11	4	57.7
RS	8	3	3	0	37.5
S	10	4	5	0	50.0
DC	7	2	2	0	28.6
SF	4	1	1	0	25.0
TC	2	0	1	0	50.0
HF	5	0	1	1	40.0
AC	6	0	1	0	16.6
C	9	3	3	0	33.3

were present once each. Parotitis occurred in three patients. Two patients had a perineal urinary fistula, and one had persistent though not incapacitating urinary difficulty because of an atonic bladder following combined abdominoperineal resection. Urinary bladder disturbance and infection were fairly frequent in minor degree and were not tabulated. Cerebral vascular accident occurred twice. Two transfusion reactions were recorded. One patient, admitted because of thyrotoxicosis, suddenly became obstructed completely by a previously asymptomatic carcinoma of the transverse colon. Thyroid crises followed operation for the carcinoma but responded to treatment after four days.

OPERATIVE DEATHS

Included in this group are all deaths which occurred in the hospital at or following operation. Tables XIII to XVII summarize all these deaths so that only brief comment is necessary.

Of considerable interest are the deaths due to peritonitis, which caused 35 per cent of the postoperative mortality. Four instances of peritonitis were due to leak at the suture line, in six the bowel was entered with gross soiling during the procedure, in another six, leakage and intraperitoneal soiling occurred at the site of the colostomy, and in four, various other causes resulted in the infection. Four of these deaths followed preliminary colostomy for obstruction, and two followed attempted exteriorization for sigmoid lesions performed in the presence of marked distention.

It seems apparent from these deaths that the following principles should be re-emphasized. First, a satisfactory anastomosis cannot be performed if certain cardinal points are not observed, *i e*, adequate blood supply, absence of tension, non-strangulating sutures, accurate approximation, and preoperative decompression of the bowel. Second, meticulous dissection must be carried out to avoid entering the bowel, particularly in the presence of marked inflammatory reaction. Third, an adequate blood supply is as necessary to both loops of a colostomy as to the anastomosed limbs of bowel. Fourth, parietal peritoneum and bowel wall cannot be sutured to hold up a colostomy loop without danger, and the colostomy loop should not be under tension. Fifth, definitive surgery should not be attempted in the presence of distention.

The mortality rate in 78 one-stage combined abdominoperineal resections for tumors of the rectum and rectosigmoid was 17.9 per cent, in 26 exteriorizations (obstructive resections) for lesions of segments from the transverse colon to the rectosigmoid, 29.6 per cent, in 28 resections with primary anastomosis in the same sites 10.7 per cent, and in 40 right colon resections for lesions of the cecum, ascending colon, and hepatic flexure, 10.0 per cent.

RESULTS

In the follow-up studies, deaths were due to the malignancy unless otherwise noted. The living who had resections were without known recurrence unless so stated. The results following palliative operations are shown in Table XVIII. One patient with a carcinoma of the rectum was still living after 18 months, one with a rectosigmoid lesion, 16 months, and one with a sigmoid tumor, 27 months.

The results in 183 definitive resections are shown in Table XIX. Three patients with rectal lesions died of other disease, one of melanosarcoma, one of cerebrovascular accident and one of unknown cause. Of the patients who had resection for sigmoid tumors, one died of pneumonia and streptococcal empyema, and one patient was living with recurrence. In the hepatic flexure group, one died 13 years and seven months after resection, the cause was an undifferentiated carcinoma of the kidney, and the patient had a radical mastectomy for carcinoma of the breast in the interim. Two other patients in this

group were living with recurrence. One of the patients who had an ascending colon lesion was readmitted three years after resection with intestinal obstruction. He failed to respond to nonoperative measures, and at exploration no cause for the obstruction and no recurrence could be found. His symptoms subsided rapidly after operation, but he expired, apparently of a pulmonary embolus. No autopsy could be obtained. Two patients died of other causes following resection for carcinoma of the cecum, one of a coronary occlusion one month after discharge, and one of a malignancy of the tonsil two years later. The two patients with lymphosarcoma of the rectum were not operated upon. One died preoperatively of urinary tract infection and uremia. The other was given irradiation therapy and died of a cerebrovascular accident 33 months later. The patient with lymphosarcoma of the cecum was living 10 years after resection, and the patient with the unclassified sarcoma of the cecum was living four and one-half years after operation.

CONCLUSIONS

- 1 Early diagnosis of malignant lesions of the colon and rectum is one of the most important factors in increasing resectability. Such early diagnosis depends primarily on adequate investigation, mainly by simple, readily available means, when suspicious symptoms such as change in stool or bowel habit and abdominal pain are encountered.

- 2 Intestinal obstruction is a complicating factor requiring careful consideration and individualized treatment.

- 3 Appropriate measures must be utilized preoperatively to correct fluid and electrolyte balance, hypoproteinemia, vitamin deficiency, and anemia.

- 4 Improved surgical technic, blood replacement at operation, better anesthesia, the antibiotic and chemotherapeutic agents and gastro-intestinal intubation are advances in treatment which have decreased morbidity and mortality.

- 5 Resection and primary anastomosis for lesions of the colon, and combined abdominoperineal resection for tumors of the rectum are at present the procedures of choice at this hospital.

Note: The author wishes to express his gratitude to Dr. Deryl Hart for his help and encouragement during this study.

THE MANAGEMENT OF MASSIVE GASTRODUODENAL HEMORRHAGE*

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THE TERM MASSIVE HEMORRHAGE implies rapidly progressive exsanguination and if its use were restricted to the description of a very specific clinical picture, much of the confusion and conflict of ideas on the subject might be avoided.

Hemorrhages from gastric or duodenal ulcer are commonly mild or moderate in severity and, in most instances, produce melena without hematemesis. Two ounces of blood are sufficient to produce a tarry stool.⁹ Yet a pint of blood may be lost into the intestine over a period of several hours without producing any clinical symptoms whatever. The designation "Massive Hemorrhage," however, should be applied to a rapid loss of blood of such proportions as to cause unmistakable hemorrhage shock.

PATHOLOGY

Gastric, duodenal, and anastomotic ulcer are responsible for approximately 85 per cent of the gross hemorrhages from the upper digestive tract.^{5,10} The fatal type of bleeding usually originates in a posterior penetrating duodenal ulcer or a penetrating ulcer of the lesser curvature of the stomach. While persistent slow bleeding generally comes from an erosion of the smaller arteries and veins of the submucosal plexus, massive hemorrhage is invariably arterial in origin and follows erosion of vessels of large calibre, usually the superior pancreaticoduodenal or the right or left gastric arteries or their major branches. In the base of the ulcer crater, as exposed at operation or autopsy, one finds the eroded stoma of a thickened sclerotic artery. It may be partly or completely occluded by a clot. Fixed in surrounding dense scar tissue the eroded vessel cannot retract, thus defeating nature's most efficient mechanism for arterial hemostasis. As the occluding clot is digested or dislodged, the bleeding recurs. Occasionally no ulcer is found in the specimen and the source of bleeding may be invisible to the naked eye. In two of our cases the bleeding vessel, without any gross ulceration, was found concealed between adjacent folds of mucous membrane. Heuer¹⁵ reported a fatal case in which the pathologist, failing to find any erosion of the mucosa of the stomach or duodenum, injected the gastric artery with saline from a pressure bottle and observed a jet of fluid from the mucosal lining. Serial sections of the area showed a small ruptured aneurysm concealed by overlying mucosal folds.

The effects of severe acute anemia and sustained hypotension upon various organs and tissues are well known but deserving of comment, and are worthy

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of more emphasis than they have received. The *immediate* effect of a rapid diminution in blood volume and hypotension may be acute circulatory failure or acute forward failure of the heart. When the blood pressure falls below a certain critical level the vasoconstrictor center, suffering from impaired blood supply, becomes weakened and loses its tone, resulting in further decline in blood pressure. The medullary centers may become irreparably damaged as a result of inadequate nutrition. *Prolonged hypotension* with qualitative as well as quantitative alterations in the circulating blood will produce changes of a serious nature in all of the vital organs. Cerebral anemia leads to cerebral anoxia manifested by stupor, dulling of the sensorium, and coma. Convulsions may be observed and a bilateral or unilateral Babinski sign may be found. Damage to the heart is indicated by the development of embryocardia or gallop rhythm with rapid appearance of pulmonary edema and death. The patient may complain of anginal pain, the result of acute coronary insufficiency, and such insufficiency may result in localized areas of necrosis or even gross myocardial infarction. The prolonged fall in blood pressure leads to diminished glomerular filtration with oliguria, anuria, rise in blood urea nitrogen and non-protein nitrogen, albuminuria, cylinduria and hematuria. Disturbances in the acid base balance of the blood may occur with hyponatremia, hypochloremia, and increased serum potassium and carbon dioxide combining power.

It is well known that severe gastroenteric bleeding produces a marked elevation of the blood urea nitrogen in eight to ten hours. Clinical observations and recent experimental investigations¹³ have shed much light on the pathogenesis of this biochemical change. The anemia per se does not seem to be a factor. Most important are the absorption of digested blood proteins and the prolonged fall in blood pressure. Either of these factors alone will produce an appreciable elevation but the combined effect of both will result in a higher azotemia of longer duration. Knowledge of the degree of azotemia in gastroenteric hemorrhage is of valuable clinical help since a sustained rise in blood urea nitrogen, in the absence of severe dehydration or pre-existing kidney pathology, is usually indicative of persistent bleeding. The blood urea nitrogen remains elevated for only 24 to 36 hours following one episode of bleeding. It has been shown experimentally¹⁹ and observed clinically⁸ that marked hyperazotemia with symptoms resembling uremia may follow sustained hypotension in severe gastro-intestinal hemorrhage and may terminate fatally. We have one instance of this among our fatal cases. A blood urea nitrogen above 100 milligrams is a very serious prognostic sign.²⁰

MORTALITY

A patient with massive gastroduodenal hemorrhage gives a history of sudden weakness, dizziness, or syncope followed immediately and almost invariably by vomiting of a large amount of blood, sometimes a loose tarry stool, but often both. He is pale, cold and sweating, slightly cyanotic, restless and complaining of thirst. The pulse is small and rapid, often above 120, the systolic pressure below 90. Blood counts and hemoglobin estimations are low.

though not necessarily an accurate index of the magnitude of blood loss at this stage, but clinical evaluation indicates an alarming acute anemia

With a picture so precise and so characteristic one should expect a reasonable conformity in recorded mortality risks. Yet, a review of a large number of reports concerned with both medical and surgical management reveals variations in mortality from 1 to 40 per cent. The discrepancy must indicate that the authors were reporting series of cases which were not comparable. Gross hemorrhage of mild degree has often been placed in the same category with massive hemorrhage. Many reports make no attempt to segregate patients into age groups and yet age, as will be shown later, is a most important prognostic factor. Combined reports of operative and non-operative management often fail to mention the stage at which surgery was performed or the type of operative procedure employed. Many reports on expectant treatment exclude from their tables the deaths following operations performed after prolonged conservative management had failed to stop bleeding. Institutions differ in the type of clinical material admitted, a hospital with an emergency ambulance service obviously received a higher proportion of the severer hemorrhages. Hospital mortality figures, of course, do not include patients who succumb to bleeding at home, and they will occasionally exclude the patient who succumbs in the emergency room before actual admission to the ward is effected.

Hematemesis is almost a constant finding in acute exsanguinating hemorrhage from penetrating duodenal ulcer and, as conceded by Meulengracht,¹⁸ is of far more serious prognostic importance than melena. Yet, in a recent analysis by Eads,¹⁰ reporting a mortality of 2.3 per cent in 129 patients treated medically for massive gastro-intestinal bleeding, there are included 94 duodenal ulcer patients, only four of whom vomited blood. A low hemoglobin and erythrocyte count certainly mean bleeding of significant proportions, but they are not necessarily indicative of hemorrhage of the acute profuse type which the term massive implies and in which there is an immediate threat to life.

Evaluation of the statistics which appear in the literature is consequently discouraging and difficult and unless reports are subjected to a most critical analysis erroneous and dangerous deductions may easily be made. However, there seem to be several significant observations on which there is more or less general agreement.

The mortality risk of hemorrhage from ulcer increases with the age of the patient. In individuals under 45 years of age the risk is obviously smaller though perhaps not nearly as slight as some reports imply. Bohrer⁴ analyzed 548 carefully documented cases of severe acute bleeding treated conservatively, all patients having a hemoglobin of 35 per cent or less and a red cell count of 2 million or less. The combined mortality of all age groups was 16.7 per cent. Bleeding gastric ulcer above age 45 showed a mortality of 28.7 per cent, below the age of 45 the risk was 20 per cent. Bleeding duodenal ulcer was fatal in 22 per cent above age 45, and in 6 per cent below age 45. This last figure, 6 per cent, is difficult to reconcile with the widespread belief that the risk to life of hemorrhage from ulcer in the younger group is negligible.

Hanson and Pederson¹⁴ found that of 393 patients with fatal hematemesis and melena in Copenhagen hospitals during the period 1915-1937, 13 per cent were under 40 years of age. Heuer,¹⁵ in analyzing the reviews of Holman, Clifton, and Cooper, all of the New York Hospital, estimates that of 337 patients admitted for severe bleeding 15 per cent were examples of fatal hemorrhage. In the older age group Blackford and Williams,² Allen and Benedict,¹ Chiesman⁶ and others, report a mortality of 25 to 33 per cent. Jankelson and Segal¹⁶ found the average age of those with fatal bleeding ulcer was 54 years. In Meulengracht's recent report¹⁸ he describes 26 fatalities and points out that 25 of the 26 patients were over 40 years of age and over half of those were over 60. Welch and Yunich²² report 125 patients with ulcer hemorrhage treated by a standard medical routine. One third had bled mildly and two thirds severely. In the group under 50 years of age the mortality was 13 per cent. Twenty per cent of those over 50 died.

Allen¹ reported that 60 per cent of the deaths in his group followed the first hemorrhage, and in Blackford's series² 78 per cent of all fatalities occurred with the first bleeding episode.

That recurring bleeding is particularly ominous is borne out by almost all reports. In this connection the comments of Avey Jones,¹⁷ are well worth examining. He expresses anxiety over cases of chronic gastric ulcer who undergo recurrent hemorrhage while in the hospital and who are over 50 years of age. In this group a single recurrence of bleeding was fatal in 50 per cent, a second recurrence was fatal in 60 per cent of the patients. In Chiesman's⁶ group of 191 patients, the mortality among 129 who bled only one day was 15 per cent while among 62 who bled 48 hours or longer the death rate was 74 per cent.

Although the mortality rate in general has been somewhat lower in females than in males of the same age group^{2, 5, 22} the risk is still great enough to caution against undue optimism in the treatment of serious hemorrhage in women.

The literature discloses only a small number of contributions from which one might evaluate the risk of surgical intervention in massive gastroduodenal bleeding. The statistical results deal in many instances with a definite type of case: the patient whose condition deteriorated steadily for many days and upon whom surgery was undertaken as a last resort. The outlook following exploration under such circumstances is too well known to require much comment. Walters²¹ states that "operative treatment in the terminal stages has proved relatively hopeless." Heuer¹⁵ reported a mortality of 70 per cent for operation after 48 hours of hemorrhage, and 10 per cent for early cases. Finsterer¹¹ reports a mortality of 29.7 per cent following surgery after 48 hours or more of hemorrhage as opposed to a 5 per cent death rate for early operation. It is only fair to note however that Finsterer's early cases included many patients who had hemorrhage of mild or moderate degree and who might have ceased bleeding under expectant treatment. This may also be true of the group of 200 patients reported by Bohmanansson³ who were oper-

ated upon during the acute stage of hemorrhage with a postoperative mortality of 52 per cent. Gordon-Taylor,¹² during the period 1933 to 1939, operated upon 18 early cases, many within 24 hours of the onset of bleeding, with one death, a mortality of 55 per cent. During the same period late operation upon seven patients was followed by four deaths, a mortality of 59 per cent.

It is obvious that little may be gained by contrasting the statistics of the proponents of medical management with the figures on surgical mortality. The groups reported, to date, at least, are not strictly comparable. The surgeon, summoned when (according to a recent report on the success of expectant treatment) "the patient is responding poorly to medical management and a fatal outcome appears likely"¹⁰ has little to start with. His results should be reported, under those conditions, not as mortality rate but in terms of the number of lives saved. On the other hand, the surgeon who operates immediately upon *all* bleeding patients may justly be criticized for subjecting to hazardous surgery many individuals who might have stopped bleeding spontaneously or upon whom operation might have been performed at a later date, if at all, with much less risk to life.

The following preliminary report from the Roosevelt Hospital is a summary of our more recent experience covering the years 1943 to 1947 inclusive, with a presentation of a plan of management and the criteria for operation.

During the five-year period from 1943 to 1947 there have been admitted to the Roosevelt Hospital 120 patients with massive gastroduodenal hemorrhage. The diagnosis of ulcer was established in 107 of these patients. In the remaining 13, an ulcer was strongly suspected but could not be proven roentgenologically.

Eighty-four of these patients were treated expectantly, and among these there were 13 deaths (15 per cent). Fifty-eight patients in this group of 84 were over 45 years of age and all but two of the fatalities were in this older group. Massive hemorrhage, treated expectantly, therefore, showed a mortality of 19 per cent in patients over 45 years old.

Eleven patients in whom bleeding appeared uncontrollable were operated upon within 48 hours of admission, with one postoperative fatality (9 per cent).

The remaining 25 patients treated surgically form a group which is too heterogeneous for accurate analysis. Operations in this group were done between the third and twenty-first day after admission. The great majority had stopped bleeding with expectant treatment and operation was performed as an elective procedure, but in three instances in which surgery was employed only as a last resort in patients who had not responded to prolonged conservative treatment, the outcome was fatal. One of these three patients had received over 10,000 cc of blood preoperatively, during a period of 12 days of expectant treatment.

Our plan of management is predicated upon the following beliefs and applies only to massive exsanguinating hemorrhage as above defined.

1 Indiscriminate emergency surgery for ulcer hemorrhage should be strongly condemned. With the few exceptions noted below, massiveness of the

hemorrhage does not constitute an indication for operation without a preliminary trial of restorative measures and expectant treatment

2 Despite the impressive reduction in mortality in recent years as a result of improved medical management, a certain percentage of patients will continue to die of uncontrollable ulcer hemorrhage

3 The risk of lethal hemorrhage in younger patients is relatively small and emergency operative intervention in this group will not often be necessary. The patient under 45 not only tolerates the effects of critical acute anemia better than the older patient, but his ulcer being often of fewer years' duration, shows less penetration and fibrosis and is thus more likely to cease bleeding spontaneously

4 All serious bleeders above the age of 45 are potential candidates for emergency operation and should be seen and followed jointly by the internist and the surgeon from the moment of admission to the hospital. The older the patient in this group, the greater the risk to life from massive bleeding

5 Severe ulcer pain preceding the hemorrhage, or persisting after the hemorrhage, is a serious symptom^{7, 12} usually indicating deep penetration, or impending or localized perforation

6 In the presence of pyloric stenosis hemorrhage is more likely to continue or recur^{11, 12} and the indication for surgery therefore becomes more urgent when such pathology is known or recognized

7 The patient over 50 bleeding from a chronic *gastric* ulcer, is the one most likely to die of uncontrollable hemorrhage^{12, 22}

8 Continued bleeding in the older age group may be considered of lethal proportions if the patient's blood pressure does not rise satisfactorily with repeated transfusions in the first 24 hours

9 Surgical intervention, when indicated, carries the least risk during the first 48 hours of active bleeding

10 In the older group recurrent severe bleeding in the patient just recovering from a previous episode is of the gravest prognostic importance

11 As a result of the profound tissue and chemical changes induced by prolonged exsanguinating hemorrhage, particularly in the older patient, the mortality from late surgical intervention is prohibitive

MANAGEMENT OF MASSIVE GASTRODUODENAL BLEEDING

1 Active treatment for the patient in shock is begun at once without subjecting the patient to any but the most cursory physical examination

2 Nothing is permitted by mouth except small sips of water or cracked ice

3 Blood replacement is begun at once. Under the most urgent conditions plasma may be employed until blood typing and cross-matching are accomplished. Plasma alone is not adequate replacement for blood

4 Blood is drawn for hematocrit, prothrombin, and blood urea nitrogen determinations, as well as for typing and blood counts

5 Repeated or continuous transfusion is required as long as the systolic pressure remains below 90 or the pulse over 130, or both. It is important to

bear in mind that pre-existing hypertension may modify these values. Since the blood deficiency at this stage is quantitative rather than qualitative, blood counts and hemoglobin determinations may not give an accurate picture of the severity of the hemorrhage.

6 When restorative measures have been initiated, a rapid physical examination is made and a history secured in an attempt to ascertain the most probable source of bleeding. Rupture of esophageal varices is common enough to warrant serious consideration in the differential diagnosis of bleeding ulcer. Less frequently a blood dyscrasia may be the cause of the hemorrhage.

7 In the absence of a definite history of ulcer in a patient who is bleeding uncontrollably, and in whom surgical intervention appears likely, every reasonable effort is made to establish a diagnosis. This should include examination of the esophagus, stomach, and duodenum by roentgen-ray if necessary. Though a patient in shock should not be subjected to this procedure under any circumstances, bleeding of itself does not contraindicate the ingestion of barium and early examination. The patient is placed in the horizontal position and the barium distributed, without palpation or pressure, by turning the patient slowly from side to side. This technic has been employed many times at the Roosevelt Hospital and though it has its obvious limitations, we have found it thus far to be without danger. Despite the fact that large clots in the stomach may at times make interpretation of films difficult or inaccurate, the examination has helped on many occasions to demonstrate suspected pathology which later was confirmed. We have not employed gastroscopy as a diagnostic procedure in the presence of acute bleeding.

8 If the presence of esophageal varices is definitely excluded a small calibre indwelling tube is passed through the nostril into the stomach, the stomach lavaged with saline and continuous suction applied. Thereafter the character of the aspirated material may furnish useful information regarding cessation or persistence of bleeding. The tube tends to inhibit nausea and vomiting and by continuous removal of gastric juice may prevent digestion and liquefaction of any clot which might have formed in the eroded vessel.

9 Opiates or barbiturates, or both, are given in doses adequate to control restlessness. Morphine occasionally produces nausea and should be given cautiously.

10 Blood pressure and pulse are recorded at half-hour intervals.

11 All fluid, amino acid, vitamin, sugar and salt requirements are met by intravenous infusion and transfusion during the period of profuse bleeding. The exsanguinating patient now under discussion rarely accepts or retains the type of food provided by the Meulengracht diet. When active bleeding ceases the patient is placed on a progressive ulcer diet with the addition of aluminum hydroxide if ulcer pain is present.

12 *Indications for Operation* When causes of bleeding other than chronic ulcer have been excluded with reasonable certainty.

a Patients over 50 years of age who continue to show a rapid pulse, drop in blood pressure, slight air hunger, and other signs of continued bleeding.

despite repeated transfusions over a period of 24 hours require surgical intervention

b Younger patients who continue to bleed profusely and who remain at shock levels despite repeated transfusions over a period of 48 hours require surgical intervention

c A recurrence of massive bleeding in the older ulcer patient demands immediate operation, delayed only by the time required for urgent blood replacement. In this type of patient procrastination may be disastrous

d Massive hemorrhage superimposed upon a known pyloric obstruction requires surgical intervention

e Simultaneous hemorrhage and perforation obviously call for immediate operation

f Patients who are first seen after many days of severe continuous or repeated hemorrhage are extremely poor surgical risks and are best treated expectantly. In this group simple high jejunostomy under local anesthesia, for feeding purposes, may be of value

OPERATIVE PROCEDURE

A patient suffering an exsanguinating hemorrhage is necessarily a poor risk. Operation should not be undertaken by a surgeon whose experience with gastric problems is limited. The complicated pathology in most of these cases, and especially in those patients who have had previous stomach surgery, will tax the skill and ingenuity of the most seasoned operator. If an experienced surgeon is not available it is more prudent to accept the hazard of expectant treatment.

It is difficult to justify palliative procedures such as ligation of vessels supplying the ulcer, simple suture of the bleeder in the ulcer bed, and gastroenterostomy alone. They have generally been found ineffective in controlling the hemorrhage. *With massive blood transfusion and modern anesthesia a patient who cannot be safely conditioned for major gastric surgery should not be subjected to the added risk of operation.*

A Partial gastrectomy including excision of the ulcer is the procedure of choice. In penetrating duodenal ulcer it may be wise, in particularly urgent cases, to open the duodenum immediately, control the bleeding by means of deep silk sutures, and then proceed with the gastrectomy. Occasionally when confronted with an ulcer which has burrowed deeply into the pancreas, it is more expedient to leave the base of the ulcer behind and perform the resection around it. The duodenum distal to the ulcer is then mobilized sufficiently to permit adequate closure of the stump. Routinely in such cases, using a single fine catgut suture, we have fixed a large soft rubber tube drain to the capsule of the pancreas in the region of the ulcer and duodenal stump.

When palpation of the stomach and duodenum fails to indicate the source of the bleeding we perform wide gastrotomy and duodenotomy, irrigate thoroughly with saline, and examine the duodenal and gastric cavities with great care. If an old gastroenterostomy is present the jejunal loops are inverted

into the stomach through the stoma and may be readily inspected through the gastrotomy. By employing this procedure we have found minute bleeding erosions which had been completely missed on palpation. If a source of bleeding is not found after thorough inspection of the duodenal and gastric mucosa, we feel that the stomach and duodenum should simply be closed. We have not encountered diffuse mucosal bleeding from simple acute gastritis but we question the advisability of gastric resection as recommended by some surgeons in such cases.

The greater the depletion of the patient before operation the more susceptible will he be to the postoperative complications common to all major abdominal procedures. Infection, retarded healing of suture lines, cardiac and pulmonary complications are seen more frequently than in elective surgery and are more lethal in their consequences. However, the liberal use of blood, amino acids, and plasma if necessary, added to the measures usually employed after elective gastric surgery, will help these patients tremendously in meeting the challenge of a very trying postoperative period.

It would be most distressing to permit the problem of bleeding peptic ulcer to degenerate into a feud between the internist and the surgeon. Obstinate adherence to any concept of therapy, be it medical or surgical, may result, unfortunately, in detriment to the patient. The aggressive surgeon who attacks every bleeding ulcer without careful appraisal of the indications for operation and the risk involved exposes himself to the same censure as the internist who permits fatal exsanguination in a patient to whom early surgery might have offered a reasonable prospect of survival. Mortality statistics, as has been shown, are too unreliable as a basis for an inflexible policy. The management of the bleeding patient must be individualized, and it should be a joint enterprise and a joint responsibility for an experienced internist and a competent surgeon. Only by the closest cooperation between them will it be possible to select from the large number of patients with ulcer hemorrhage, the relatively small group who might be saved by emergency surgical intervention.

SUMMARY

- 1 The term massive hemorrhage should be applied only to an acute, rapid loss of blood, producing hemorrhagic shock.
- 2 Prolonged, severe hypotension from acute hemorrhage may cause irreparable damage to vital organs, particularly in the older patient.
- 3 The mortality risk of hemorrhage from ulcer increases with the age of the patient, and is greater in gastric than in duodenal ulcer.
- 4 Hemorrhage is more dangerous when preceded or accompanied by ulcer pain, or in the presence of pyloric obstruction, and when bleeding recurs while the patient is convalescing from a previous severe episode.
- 5 Surgical intervention, when indicated, carries the least risk during the first 48 hours of active bleeding.
- 6 A plan is presented for the management of massive gastroduodenal bleeding, and the indications for emergency surgical intervention are discussed.

7 The treatment of bleeding peptic ulcer is the joint responsibility of the internist and the surgeon

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AN EXPERIMENTAL STUDY OF ANTIPERISTALTIC JEJUNAL LOOPS*

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SINCE THE FIRST REPORT in 1935 by Whipple, Parsons and Mullins¹⁵ of a radical resection of the duodenum and head of the pancreas for carcinoma of the ampulla of Vater, numerous modifications have been tried to overcome the difficulties which followed the initial procedure. The important complication of cholangitis led Whipple¹⁶ in 1938 to anastomose the gallbladder, and later the common bile duct, to an antiperistaltic limb of jejunum created by the Roux-Y type of anastomosis. The same type of anastomosis has been used by Allen,¹ Cole³ and others for the correction of impermeable strictures of the common bile duct.

The distressing complication of cholangitis occurs even after the modified Whipple procedure has been used, and this has stimulated interest as to the mechanism. The organism most commonly mentioned as being responsible was the colon bacillus. Numerous mechanical causes have been proposed. Wangenstein¹⁴ stressed the importance of a non-patent or stenosed stoma as an important factor in the production of cholangitis following cholecystenterostomy. Very little information is available, however, on the best length of the antiperistaltic segment of bowel to be used in the Roux-Y type of anastomosis. In reviewing the many modifications of the original Whipple operation, the authors could find only the following references to the length of antiperistaltic limb of jejunum utilized. Pearse¹² initially used a six inch loop. In later cases, this was lengthened. Dennis⁵ stated that 40 centimeters of jejunal segment were used to separate the biliary from the gastric anastomosis. His patients did not experience any postoperative cholangitis, and postoperative fluoroscopy on one of his patients "showed rapid emptying of the gastric pouch with no regurgitation into the proximal jejunal loop." Cole³ stated that the antiperistaltic limb should be at least 24 inches long when utilized in common duct surgery.

Hence, it was felt that an attempt should be made to determine the optimum length of an antiperistaltic limb of bowel. Also, that a comparison should be established between antiperistaltic limbs of jejunum and loops of jejunum "defunctioned" by an enteroenterostomy as suggested by Cattell,² Cole³ and others.

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METHODS

In order to determine the extent of regurgitation in an antiperistaltic limb of small bowel, the following experiments were performed on dogs. In the first phase of the experiment, a jejunal fistula was utilized using the method of Mann and Bollman.⁸ The abdomen was opened, the ligament of Treitz identified and divided. Approximately six inches beyond the ligament, the proximal jejunum was divided and the distal end brought out through a stab wound in the abdominal wall as a permanent stoma. A Roux-Y type of enteroenterostomy was performed implanting the proximal end of the transected jejunum into the antimesenteric border of the distal end at distances of four, eight, ten, 12, 14, 16, 20 and 24 inches from the stoma (Fig 1). Postoperatively all dogs were watched carefully for the loss of

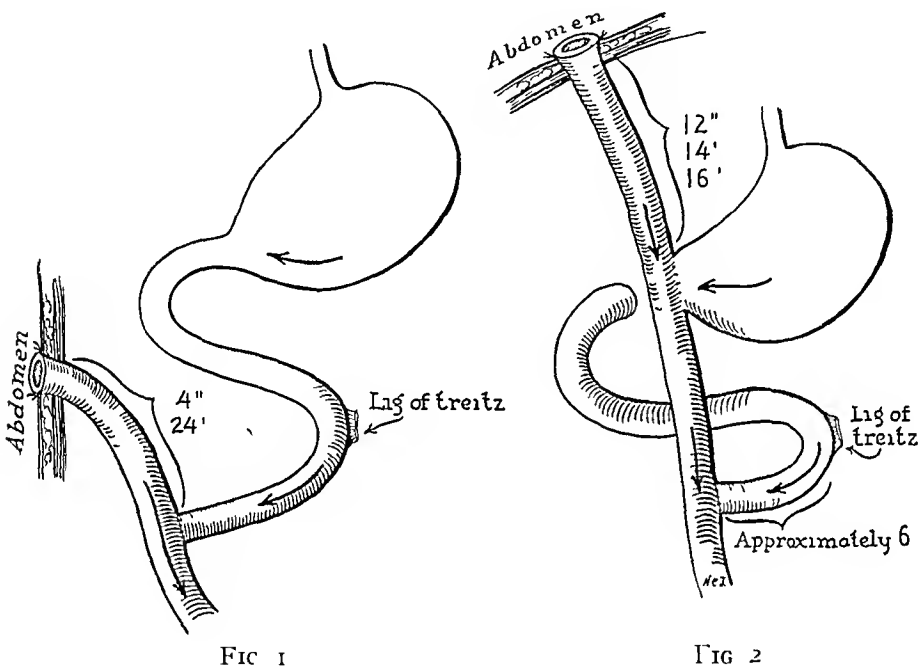


FIG 1—Jejunojejunal fistula
FIG 2—Gastrojejunal fistula

intestinal secretions through the stoma. Dye, in the form of methylene blue 0.24 Gm, was given orally and staining of the stoma recorded. In addition, some dogs were studied fluoroscopically following the administration of barium by gavage without sedation or anaesthesia.

In the second phase of the experiment, the abdomen was opened and the ligament of Treitz identified and cut. Approximately six inches beyond the ligament, the jejunum was divided, and following resection of the pyloric ring of the stomach and closure of the proximal duodenum, the distal end of the transected jejunum was brought out through a stab wound in the abdominal wall as a permanent stoma. An end-to-side gastrojejunostomy was performed,

thus creating above the gastric anastomosis antiperistaltic limbs of jejunum of 12, 14, and 16 inch lengths. The proximal end of the transected jejunum was reimplanted into the distal segment approximately six inches below the gastric anastomosis. Figure 2 which illustrates the second procedure closely simulates that seen in Whipple's article of June, 1946¹⁸ "showing antecolic or postcolic anastomoses with an antiperistaltic limb of resected jejunum." In our experiments no biliary anastomoses were performed, nor were the pancreas and duodenum extirpated.

In the third phase of the experiment, the abdomen was opened and the ligament of Treitz identified. Approximately eight inches from the ligament an enteroenterostomy was performed, the stomata being eight centimeters in length, creating "defunctioned" loops 24, 32, and 48 inches in length. The mid point of the loops was brought out through the incision and sutured to the wall. After closing the incision, an opening was made in the bowel wall creating a permanent stoma as illustrated in Figure 3.

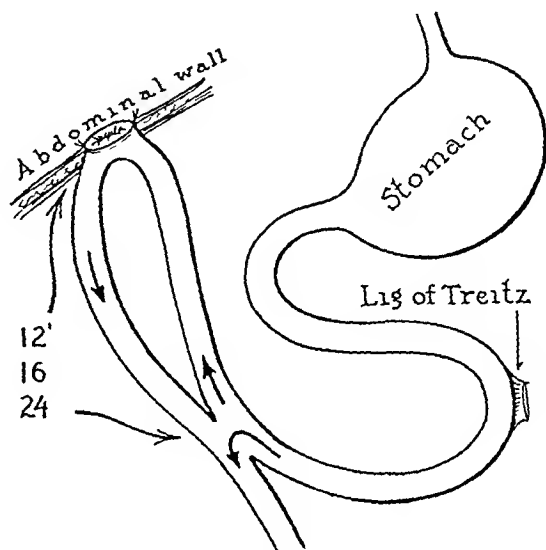


FIG 3—Fistula of jejunal loop "defunctioned" by a jejunojejunostomy

DISCUSSION

Table I summarizes the first group of experiments where variable lengths of antiperistaltic jejunal fistulae were used. It is noted that in addition to a dye given orally, the material constituting the intestinal stream will regurgitate up an antiperistaltic limb ten inches in length. Fluoroscopically, following the introduction of barium by gavage, the barium was not seen to traverse an antiperistaltic limb eight inches in length, but 15 minutes later appeared at the stoma. Observations of limbs 12 and 14 inches in length showed the barium to enter the limb readily for a distance of six inches. Postmortem examination of all of these dogs failed to reveal the presence of ulcerations in the mucosa about the stomal sites.

Table II summarizes the results in the second group of experiments where gastrojejunal antiperistaltic limbs were utilized. The minimum length of limb used was 12 inches on the basis of the previous experiment. Because of the more forceful evacuatory contractions of the stomach, it was surmised that a limb 12 inches in length would be too short. However, as noted, neither dye nor intestinal juices appeared at the stoma of a 12, 14 or 16 inch limb. Fluoroscopically the barium entered both 12 inch limbs for a distance of five to six inches (Fig 4). In one instance, the barium disappeared from the limb with the appearance of peristaltic waves. However, in the other case,

the barium persisted as a thin line despite vigorous contraction waves down the limb. Postmortem examination revealed the presence of ulcers in the 14 and 16 inch limbs in the jejunum just opposite the gastrojejunostomy stoma (Fig 5-Fig 6) when sacrificed 50 days and 45 days postoperatively respectively. This closely simulates the work and findings of Mann and Williamson⁹ in one phase of their classical experiments on the production of peptic ulcers.

TABLE I—*Antiperistaltic Jejunojejunal Fistulae*

Dog Number	Length of Antiperistaltic Limb	Presence of Intestinal Juices	Presence of Dye	Remarks
47-62	4"	Profuse brownish green in 6th postoperative day	None seen	Dog died 10 postoperative day of peritonitis
47-65	8"	Questionable	None given	Dog sacrificed on 5th postoperative day because of distemper
47-77	8"	Small amount of intestinal juice on 6th postoperative day	None given	Dog died on 6th postoperative day. Perforation at suture line
47-83	8"	Scant fecal material noted	None	Given barium p o and fluoroscoped 15 minutes later barium appeared at stoma. Loop lengthened to 24"
47-204	10"	Some gas and scant fecal material	Yes	Dog sacrificed 2 weeks p o. Did poorly. Chronic bilateral glomerulonephritis and nephrosis
47-222	10"	Slight on 6th p o day	None	
41-50	12"	None	None	
Short, black female cocker	12"	None	None	On fluoroscopy barium readily entered antiperistaltic limb for distance 6". None at stoma
47-162	14"	None	None	
40-34	16"	None	None	
41-53	20"	None	None	
47-83	24"	None	None	

Table III summarizes the results of the third group of experiments where loops of jejunum were utilized which had been "defunctioned" by means of an enteroenterostomy. Loops with 12-inch limbs were much too short. Despite a wide, patent enterostomy stoma, all of these dogs died within eight days from the time of operation. Dye and intestinal secretions literally poured out of the stomata. The deaths may be attributed to loss of fluids and electrolytes from a high fistula similar to that of a high intestinal obstruction.¹⁰ The loop with a 16 inch limb was still too short to prevent loss of intestinal juices. The loop



FIG 4—Arrow designates anti-peristaltic limb of jejunum containing barium



FIG 5—Ulcer on posterior wall of jejunum opposite the gastrojejunostomy stoma

with a 24-inch limb, although it prolonged the dog's life, was unsuccessful in completely diverting the intestinal stream ,



FIG 6—Photomicrograph of ulcer of Fig 5 $\times 125$

TABLE II—*Antiperistaltic Gastrojejunal Fistulae*

Dog Number	Length of Antiperistaltic Limb	Presence of Intestinal Juice	Presence of Dye	Remarks
48-27	12"	None	None	Fluoroscopically showed regurgitation into antiperistaltic segment for 4-5 inches Sacrificed 78 days p o No ulcers noted
48-63	12"	None	None	Barium entered limb readily for 4 inches Sacrificed 56 days p o No ulcers noted
48-5	14"			Dog died 2nd p o day Acute dilatation of stomach
47-235	14"	None	None	At post mortem ulcer noted on posterior wall of jejunum opposite gastrojejunal stoma (50 days p o)
47-164	16"	None	None	Ulcer noted same as above (45 days p o)

CONCLUSIONS

- 1 In dogs regurgitation occurred for a distance of ten inches in an antiperistaltic limb of jejunum created by a Roux-Y type of anastomosis
- 2 The optimum length for the antiperistaltic limb of a Roux-Y type of

anastomosis was found to be 12 inches. This prevented regurgitation of dye, barium or intestinal contents out of the stoma.

3. No difference was noted in the extent of regurgitation in an antiperistaltic limb created by a jejunojejunostomy or a gastrojejunostomy. Hence, the important factor was the length of the limb, and the force with which material entered the loop was apparently of lesser significance.

TABLE III—"Defunctioned" Jejunal Loop Fistulae

Dog Number	Length of Ascending Limb of Loop	Presence of Intestinal Juice	Presence of Dye	Remarks
47-172	12"	Profuse	Yes	Died 7 p. o. day
48-10	12"	Profuse	Yes	Died 8 p. o. day
48-14	12"	Profuse	Yes	Died 7 p. o. day
47-209	16"	Some discharge daily from stoma	Yes	Alive at end of 18th p. o. day. Sacrificed. Dye given day previously stained entire ascending loop.
48-34	24"	Slight discharge	Slight staining	

4. The use of loops longer than 12 inches in a gastrojejunal Roux-Y anastomosis resulted in peptic ulcer formation.

5. An enteroenterostomy between loops of jejunum does not short-circuit these loops. The enteroenterostomy does not divert all of the intestinal stream even when the limbs of the loops are 24 inches in length.

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SYMPATHECTOMY IN PERIPHERAL ARTERIOSCLEROSIS†

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THE ENORMOUS TOLL taken by arteriosclerosis is still appalling and probably less progress has been made in this field than in any other in medicine. For this reason, any therapeutic method which offers the hope of staying its inexorable course should be seized upon vigorously until its possibilities have been exhausted and what it has to offer has been adequately tested and evaluated.

Considered a "degenerative" disease, arteriosclerosis has been accepted by the profession as the almost inevitable destiny of those who live long enough. It is the invariable cause of death when some intercurrent disease does not strike first. In a large number of cases it causes inestimable disability and distress long before the capital stroke is administered. In the lower extremities, obliterative vascular sclerosis is so rampant a scourge that otherwise vigorous men are incapacitated to a varying degree by it for many of the last years of their lives. From mild to disabling claudication to actual loss of one or more limbs is the terrible tribute it demands, and little has been offered to interrupt its relentless progression.

Almost universally the use of sympathectomy had been decided in the treatment of what was accepted as a progressive, organic, irreversible process. Only when angiospastic phenomena played a significant role, it was thought, could the operation help, and to use it for arteriosclerosis obliterans would serve to discredit it in the indicated situations. Yet scattered reports suggesting its usefulness in selected cases of obliterative vascular sclerosis began to appear in the literature about 1935. In that year, Harris reported good results from the procedure in 5 of 12 cases. The material included patients not tested preoperatively and those with poor responses to testing. He concluded that sympathectomy was of value in obliterative vascular disease when spasm accompanies it and that all patients showing a rise in skin temperature following block would be helped. In 1936, Leiche reported that 76.4 per cent of his sympathectomized arteriosclerotics were improved. The subject was again discussed by Atlas in 1941 in an article based upon 12 selected cases of arteriosclerosis treated by sympathectomy. All lost the sensation of cold numb feet that had been present preoperatively. Ulcers which were present in two cases healed, and intermittent claudication disappeared in seven of nine cases in which it had been present. All, preoperatively, had severe subjective and objective evidence of circulatory deficiency on an arteriosclerotic basis but by

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sympathetic block indicated that the collateral vascular pathway was capable of hypertrophy. In 1937, Pearl recommended lumbar sympathectomy in the treatment of angiospastic claudication. His conclusions were based upon the response of six cases to vaso-motor paralysis. Three of the cases showed evidence of organic arteriosclerotic disease in addition to the angiospastic phenomena. In 1942 Freeman and Montgomery reported on 12 cases with peripheral arteriosclerosis and intermittent claudication. All but one showed evidence of obliteration of the major arteries of the leg. Seven responded to sympathetic block with objective evidence of increased ability to work while three others were subjectively improved. Six of the first group were subjected to lumbar sympathectomy with immediate and persistent relief.

Trimble in 1944 published his results in 24 cases of peripheral arteriosclerosis treated by sympathectomy. Only three of the cases were not improved. These had gangrenous ulcers and came to amputation. Eight were greatly improved, the remainder moderately so. Eleven cases with ulceration or gangrene went on to complete healing. The degree of obliteration which was present is indicated by the fact that 16 had no pedal pulses, six only a faint unilateral pulse, one a faint bilateral pulse, and in one there was no record.

In March of 1946 Telford and Simmons reported on a series of 88 cases which were treated by sympathectomy. Most of these did not have preliminary testing by nerve block and hence were unselected. In 47 cases the operation was performed for severe intermittent claudication. All showed improvement although it was striking in only six which have been almost normal since operation. Not one, however, followed for five to 15 years, developed rest pain or gangrene. Forty-one cases had incipient or frank gangrene. In 21 the results were good with abolition of rest pain and a change from chronic invalidism to reasonable activity with separation and healing of the gangrenous areas. Twenty cases did come to amputation, but frequently at a lower level.

Later in 1946 de Takats gave a simple, logical rationale for the use of lumbar sympathectomy in selected cases of peripheral vascular sclerosis. Encouraged by the above reports and by the response in a case of his which preoperatively was thought to be thromboangitis obliterans but which at operation proved to be arteriosclerosis, he reversed his previous stand of recommending sympathectomy only for angiospastic states and performed the procedure in 25 selected cases of obliterative vascular sclerosis. The results were extremely good. In one group a dramatic increase in walking ability occurred, in a second amputation was averted, in a third group amputation could be performed at lower levels, while in a fourth intractable neuritic pain of the causalgic type was benefited. The rationale for the procedure was the release of normal vasomotor tonus insuring an even bloodflow uninfluenced by anything but the metabolic needs of the tissues. The sympathectomized extremity was freed from the influences of cold, of emotion, and of standing. By 1947 his series had been expanded to include 57 cases 53 of which had

been benefited by the procedure. In discussing de Takats' 1947 paper Pearl reported that 50 arteriosclerotic extremities were improved by sympathectomy at his clinic. In about one-third of the cases the peripheral pulses showed an increase in volume or an appearance where before operation it was absent. About one-third were relieved of claudication and in many the color changes characteristic of circulatory deficiency disappeared. Not one came to amputation while in the same period of time 75 low thigh amputations were performed in a comparable series of non-sympathectomized extremities.

These encouraging reports have caused surprisingly little stir. Besides the de Takats' paper, no other article on sympathectomy for peripheral arteriosclerosis is to be found in the 1947 literature. The general attitude is still defeatist, the senescence theory still prevalent, the recommendations for treatment found in the recent literature still are primarily medical (diethyl ether,¹⁰ hypertonic saline,⁶ histidine and ascorbic acid,¹⁸ tetraethyl ammonium bromide,¹⁹ alpha tocopherol,¹⁵ etc.) It is because of this that another paper stressing the value of sympathectomy in selected cases of obliterative vascular sclerosis is not out of place. The following series, while small, is highly illustrative, and may possibly help to stimulate interest in the field.

CASE MATERIAL

Eight lumbar sympathectomies were performed upon six patients. All had advanced states of peripheral arteriosclerosis with manifestations varying from intermittent claudication to frank gangrene with or without infection. In seven instances definite benefit resulted. In one, in which gangrene had spread to beyond the middle of the foot all that was hoped for was to make possible healing of an amputation at a mid-leg level. This was achieved but of course it cannot be concluded that the sympathectomy was responsible. A summary of the cases will be given which will be followed by a more detailed discussion.

Case 1—V. A., Sydenham Hospital No. 103854, was a 56-year-old male diabetic admitted on June 22, 1946, with a moist ulcerative gangrenous lesion about 3 by 2 inches on the dorsum of the left foot extending onto the great toe and to a lesser extent onto the other toes. The extensor tendons were exposed in the base of the ulcer. A gangrenous bleb was also present over the great toe of the other foot. Both feet were cold with dependent rubor and marked blanching on elevation. Only the right popliteal and femoral pulses were palpable. Oscillometric readings were less than 10 bilaterally. The histamine flare and saline absorption tests showed extremely poor collateral circulation. There seemed to be no hope for the left leg and mid-thigh amputation would have been proceeded with immediately were it not for the lesion of the right great toe which placed that limb in jeopardy as well. Because of this it was decided to employ conservative treatment until such time as the fate of the right extremity clarified. Until July 15th bed rest, wet dressings, and anti-diabetic therapy were employed. The ulcer of the left foot became larger and dirtier and the gangrenous bleb of the right great toe extended to involve most of the toe. On July 16th daily bilateral lumbar sympathetic blocks were added to the treatment. Objective and subjective warming of the members was noted which, after the first few days, persisted for progressively longer periods until after about ten days its effect lasted practically around the clock. By the 1st of August a remarkable change in the ulcer was noted, it had become clean, and was beginning to granulate and to epithelialize in from the edges. The histamine and saline absorption tests now showed

an improved collateral circulation and on the right oscillometric readings were improved. By the 21st, the ulcer was definitely smaller and both the right and left great toes were demarcating. With the ultimate successful result now almost assured, left lumbar sympathectomy was performed on August 21st. At the patient's request, because the left leg felt so much better than the right, this was followed by right lumbar sympathectomy on September 6th. By September 16th the ulcer was healed, both great toes had demarcated and the patient had no pain, even, as was learned, when contrary to orders he walked about the ward. Of remarkable interest was that a dorsalis pedis pulse was now palpable bilaterally. The left great toe was eased off and the patient was discharged on October 11th. In December, 1946, he was readmitted for the removal of the right great toe. The left foot was healed at the time, the right went on to healing shortly after the toe had been amputated.

The patient returned to useful activity. He was readmitted in June, 1947, for a pressure ulcer of the plantar surface of the left second toe with purulent exudate extending through the toe to the dorsum. This toe was amputated with prompt healing following. There has been no further trouble of any sort since.

Case 2—M. M., Mt. Sinai Hospital No. 553291, was a 61-year-old female diabetic admitted on August 23, 1946, with gangrene of the right great toe and severe cellulitis of the remaining toes and of the distal half of the foot. There had been a left mid-leg amputation a year before for gangrene. Marked peripheral arteriosclerosis was present with no pulses palpable in the foot. The right popliteal pulse was faintly palpable. Oscillometric readings were markedly reduced. No hope was held for the limb, but because the other had already been lost, an effort to save this one was made. Treatment consisted of bed rest, wet dressings, penicillin, and daily sympathetic blocks. The cellulitis receded and some improvement in color and increased warmth of the foot occurred. An alcohol lumbar sympathetic block was done to provide a more permanent effect. The right great toe was then amputated, leaving a dirty base containing considerable slough. Infection and gangrene extended to the remaining toes which were successively amputated. Tendon and soft tissue slough persisted in the base of the wound but no longer seemed to be spreading. The alcohol block, the effect of which was wearing off, was repeated, with return of the warming of the foot that had been obtained previously, and on two occasions the wound was debrided of accessible slough. No further extension of gangrene or infection occurred and by late November the wound was finally clean and granulating. On December 12, 1946, she was transferred to a City hospital. Here on January 9, 1947, a left lumbar sympathectomy was performed as the effects of the alcohol block had again worn off. The foot was considerably warmer after operation. Healing progressed favorably and was complete by March 15, 1947, when the patient was discharged. The stump has remained well healed since.

Case 3—B. L., Beth David Hospital No. 46-4386, was a 65-year-old diabetic admitted with a six-month history of intermittent claudication and rest pain in the right foot. Marked obliterative vascular sclerosis was present, both feet were cold and discolored reddish-purple, the right more so than the left. Both popliteal pulses were palpable but none distal to these. Upon right sympathetic block the pain was relieved but only slight warming of the foot was obtained. Courses of etamon and of diethyl ether were given but gangrene of the third toe of the right foot developed in spite of these. The toe was amputated after demarcation had occurred but sloughing tendon was seen in the base and some cellulitis was present proximal to it. Roentgen-ray showed marked calcification of the vessels and the limb's coldness extended up to the mid-leg. Lumbar sympathectomy was advised but was refused. Rapid extension of the gangrenous process took place to the second toe and the adjoining sole of the foot. This toe was amputated and the wound debrided but gangrene promptly extended to beyond the middle of the sole. At this time the popliteal artery was no longer palpable. It was obvious that

there was no hope for the leg but sympathectomy was again advised in the hope that it would make it possible to save the knee. Consent was given this time and on March 8th, 1947, the 2nd, 3rd and 4th right lumbar ganglia and intervening chain were resected. Within a few days the level of gangrene seemed to demarcate although the base of the wound remained dirty. Histidine and ascorbic acid were tried without effect. On April 10th mid-leg amputation was performed. At operation all major vessels were seen to be occluded but nevertheless the color of the muscle was good and fair bleeding was observed from the small vessels in its cut surface. The stump was closed primarily without drainage and primary healing was obtained.

The patient was discharged, ambulatory on crutches on May 21, 1947. In August, 1947, despite his age, he was fit with a prosthesis. With this and a cane he managed quite satisfactorily but unfortunately gangrene of the left foot developed in November. Studies before and after sympathetic block indicated that no improvement could be anticipated from sympathectomy. The gangrene advanced and mid-leg amputation was performed on November 19, 1947. Primary healing was not achieved. Healing by secondary intention progressed slowly until in April, 1948 only a superficial 10 cm crusted area remained unhealed. Despite this he was fit with a second prosthesis and not only has he learned to walk with the two artificial limbs, but he has found part-time employment as a cashier. As of June, 1948, the right stump is soft, pliable and asymptomatic, while the unhealed area on the left is smaller and slowly completing its healing.

Case 4—J T, Sydenham Hospital No 102001, was a 66-year-old male diabetic who had been in another hospital in February, 1947, in diabetic coma, and with a slight infection of the right great toe. He was discharged with the infection incompletely cleared and was admitted to Sydenham Hospital on March 14, 1947. His temperature was 105 degrees. The right great toe was gangrenous with marked local suppuration and cellulitis extending over about half the dorsum of the foot. There was marked peripheral arteriosclerosis. The right foot, despite the cellulitis, was colder than the left. No pulses were palpable in the right foot but the popliteal artery was palpable. Severe diabetic acidosis was present. Penicillin was given and the acidosis controlled by appropriate measures. Histamine flare and saline absorption tests showed extensive impairment of the collateral circulation. Lumbar sympathetic block was done with an excellent response, the foot becoming appreciably warmer.

Right lumbar sympathectomy was performed on March 21st, excising the chain from below the first lumbar to above the fourth lumbar ganglia. The foot after operation was definitely warmer. Following the procedure, the necrotic skin of the gangrenous toe was excised without anesthesia on the ward. About a half ounce of pus was evacuated. Necrotic extensor tendons were seen in the base of the cavity. On April 7th the great toe and the distal half of the first metatarsal were amputated and the soft tissue debrided. Healing was complete by the 9th of May on which day the patient was permitted to walk without crutches.

Case 5—N L, Beth David Hospital No 47-2072, was a 59-year-old man admitted on May 16, 1947, with a history of progressive coldness and numbness of both feet and severe pain in the left foot and leg on walking. He had been given a course of histidine and ascorbic acid at another hospital not only with no relief but with progression of the pains to a degree where they were present even at rest.

There was marked peripheral arteriosclerosis. Roentgenogram of the leg showed calcification of the arteries. The feet were cold and moist with dependent rubor and ischemia in the elevated position. Neither dorsalis pedis nor posterior tibial was palpable. Both popliteal pulses were diminished. Oscillometry showed markedly reduced readings bilaterally. Orthopedically the feet were bad, there was bilateral hallux valgus, marked pes planus, and the second toe overlapped the great toe of each foot. He stated, however,

that these findings had no relation to his complaints. Upon left lumbar sympathetic block increased warmth and complete amelioration of symptoms resulted.

On June 13, 1947, the left lumbar sympathetic chain was excised from below the first to above the fourth lumbar ganglia. Following this procedure pain disappeared entirely and definite warming of the member was achieved. He was discharged on June 26th walking well. There was insufficient subjective symptomatology referable to the right lower extremity for sympathectomy on this side at the time.

The patient has been seen on several occasions since the operation, the last on March 9, 1948. The increased warmth of the left leg and foot persists and he is now able to walk any distance required by his normal activity (up to ten blocks) without pain.

Case 6—I. H., Mt. Sinai Hospital No. 575474 was a 55-year-old male private patient admitted on January 16, 1948, with a history of intermittent claudication in the left leg for five years. This had progressed to a degree where he was unable to walk more than a block before it set in. He had sold his car because cramps developed in the left calf after driving a short distance. On examination there was marked peripheral arteriosclerosis with absence of the posterior tibial, dorsalis pedis and popliteal pulses on the left. All were palpable but diminished on the right. Both feet were cold, with dependent rubor, more marked on the left. Oscillometric readings were practically absent from the left leg and markedly diminished on the right. Histamine flare and saline absorption tests showed marked impairment of the collateral circulation. Roentgenograms showed calcification of the vessels. The response to left posterior tibial nerve block was excellent with marked warming over the area of distribution of the nerve.

Left lumbar sympathectomy was performed on January 17, 1948, excising the chain below L-1 and above L-4. The result was phenomenal. Within ten days after operation the patient walked eleven blocks, at which time he developed claudication in the opposite calf and fatigue of both thighs. At his request right lumbar sympathectomy was performed on January 28th. The result was again excellent.

The patient was seen last on May 5th, 1948, at which time his legs and feet were warm and dry and he was able to walk almost limitlessly without claudication until fatigue or boredom caused him to stop. About 12 blocks was the distance of his usual walks and not infrequently this was extended to more than a mile.

DISCUSSION

In the above series, eight lumbar sympathectomies were performed upon six patients with advanced, symptomatic peripheral arteriosclerosis. Although the series is small, the variety of lesion included represents a cross section of those that may be encountered. In all cases, the degree of sclerotic vascular obliteration was severe, with both subjective and objective evidence of marked circulatory deficiency. In only one of the eight extremities were pulses in the foot even faintly palpable. Gangrene, with or without ulceration and infection was present in five instances. Despite the advanced degree of organic change and the complicating lesions definite benefit was achieved in seven of the eight cases, and limbs were saved that would otherwise probably have been lost.

Incapacitating intermittent claudication was the indication for sympathectomy in two cases (Cases 5 and 6). In both, the feet were cold and moist, with dependent rubor and blanching on elevation. Their response to block was good. Both achieved remarkable relief from sympathectomy, unilateral in one, bilateral in the other. Case 5 now walks up to 10 blocks and severe rest pain and the sensation of coldness of the limb have also been relieved. In Case 6

the capacity to walk has been increased from about a city block to an indefinite distance. Sympathectomy was performed on the second side at the patient's request as after its performance on the side of which he originally complained, his ability to walk increased to such a degree that intermittent claudication developed on the previously better side.

Cases 1, 2, and 4 were admitted with gangrene of one or more toes and accompanying infection. In addition, Case 1 had a large dirty ulcer over the dorsum of the left foot with exposure of the extensor tendons in the base of the ulcer. In all of these, after sympathectomy, only toes were lost, with relatively asymptomatic use of the remainder of the member. This was of particular importance in Case 2 where one leg had already been amputated.

Only in Case 3 is it questionable whether anything was accomplished since at the time that sympathectomy was performed extensive spreading gangrene of the foot was present and it was already accepted that the limb could not be saved. The purpose of sympathectomy in this case was to lower the level of the necessary amputation from above the knee to the mid-leg. Incidentally, in this case, various medical methods of treatment had been unsuccessfully tried before sympathectomy was permitted. Despite the occlusion of all major vessels demonstrated at operation, primary healing was obtained, obviously the result of an increased collateral circulation. While hardly conclusive, it is possible that this primary healing at the mid-leg level was attributable to the preliminary sympathectomy, particularly since on the other side, later amputated without sympathectomy, primary healing was not obtained.

The question of the propriety of attributing the results that were obtained to sympathectomy may be raised. The experimental work of certain investigators indicates that the blood supply to the muscles of the leg is not directly controlled by the sympathetic nervous system (Grant, Friedlander, Silbert and Bierman) and on the basis of such data it has been stated that results achieved are independent of the operation. On the other hand experimental work by Grimson and Shen indicates that the blood vessels of skeletal muscles do react to vasomotor impulses by vasoconstriction and dilatation. This was demonstrated on both normal and skinned limbs, showing that the vasomotor phenomena occurred equally well in both. If this is the case, sympathectomy would result in the elimination of whatever vasoconstrictor phenomena were present and promote healing.

I do not feel, however, that it is essential to analyze the validity of experimental work on vasomotor influence upon blood flow to the extremities in an effort to predict what the effect will be in humans with vascular disease. This is particularly so since there is a fairly large body of clinical material which gives, to my mind, indisputable evidence that circulation has been improved by the procedure (*vide supra*). While a decided increase in basal blood flow may not be expected after sympathectomy, as de Takats points out, fluctuations in blood flow due to influences of cold, standing and emotion do occur even in limbs with marked obliterative sclerosis and these are unquestionably eliminated. He demonstrates by oscillometric graphs before sympha-

thectomy the existence of such vasoconstrictor phenomena, and the elimination of these after sympathectomy. Moreover, both clinical examination and the usual circulatory tests have demonstrated an improvement in the circulatory status after sympathectomy both in our series and in those of others, even to the appearance of pulses which were absent before operation. And why it should be accepted that vasoconstriction operates in thromboangitis obliterans if the blood supply to the leg muscles is independent of the sympathetic system, yet not in arteriosclerosis, is difficult to understand.

The most striking evidence, however, is contained in the clinical results in the body of case material which has been accumulated. In his discussion of de Takats' article, Ochsner states that the functional result is more important than oscillographic recordings. It is indeed difficult to attribute the disappearance of intermittent claudication after sympathectomy to anything other than the operative procedure, presuming, of course, that there has been a follow up of sufficient length to show that the result obtained is not evanescent. Insofar as the ulcerative and gangrenous lesions in our series are concerned, while it is of course possible that these might have gone on to healing without sympathectomy, as a rule lesions such as those described almost invariably come to major amputation. This was avoided in all but one of our cases, a case in which sympathectomy was done not with any hope of saving the foot but merely to insure the success of amputation at the mid-leg level. These results, I must add, are no longer novel and are simply corroborative of a much larger volume of material already referred to.

The various non-surgical methods of treatment of circulatory deficiency in peripheral arteriosclerosis (diethyl-ether, histidine and ascorbic acid, tetraethyl ammonium bromide, alpha tocopherol, etc.) have not seemed to have any comparable benefit in our hands. The operation itself, utilizing the Pearl approach as described by de Takats, is an extremely bland one with little or no mortality. It rarely takes more than a half hour to 45 minutes even in obese individuals and disturbs the patient less than a simple appendectomy. Naturally, preliminary testing by sympathetic or peripheral nerve block serves as the basis for selection of cases for the operation. Alcohol sympathetic block is not to be recommended as its effect is frequently incomplete and impermanent, and serious complications are not uncommon.

In conclusion I should simply like to reiterate the purpose of this report which is again to call attention to the fact that a simple operative procedure offers hope for staying the course of an otherwise dread progressively incapacitating malady. The reported results have been good out of proportion to the degree to which the profession at large has indicated their willingness to make use of the procedure. It is in the hope that a more widespread utilization of lumbar sympathectomy in the treatment of selected cases of peripheral arteriosclerosis will result, that this report is made.

SUMMARY

1. The literature on the use of lumbar sympathectomy in the treatment of obliterative vascular sclerosis is reviewed.

- 2 A series of eight extremities with advanced, symptomatic, complicated lesions treated by lumbar sympathectomy is presented
- 3 The rationale and efficacy of the procedure are discussed, and an appeal for its trial in selected cases made

ADDENDUM Since this article was submitted for publication two cases with sufficient follow up are to be added to the series. One was a private patient of Dr Morris Steinberg, a 54 year old male diabetic and arteriosclerotic, who developed an area of gangrene on the heel of a cold, pulseless extremity. The gangrenous area healed completely following lumbar sympathectomy. The second was a private patient of Dr Henry Dolger. This was a 65 year old woman with diabetes and arteriosclerosis who had been completely incapacitated by a popliteal artery embolus six months previously. The limb was pulseless and cold and there was pain even at rest. Following left lumbar sympathectomy, the color and temperature improved, the pain disappeared, and the patient is now able to walk five blocks without appreciable effort or distress.

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TISSUE REACTION TO PLASTICS USED IN SURGERY WITH SPECIAL REFERENCE TO TEFLON*†

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SURGEONS' INTERESTS in plastics have been confined in the past to its application as suture material. The increasing use of internal prosthetic devices has made surgeons more aware of the adaptability of plastics to these problems.

Plastics have been used to fill in bony defects in reconstructive and maxillo-facial surgery, to replace missing segments of calvarium in neurosurgery, in replacing large defects of the thoracic cage, as a non-suture device in blood vessel anastomosis, to replace large segments of vessels experimentally, as blood vessel catheters, and in a host of other applications. Since the majority of the plastics that have been investigated are non-absorbable, the limiting factor to their use would be the production of tissue reaction.

The factors which cause tissue reaction in non-absorbable plastics can be attributed to their chemical and physical properties. Chemical inertness and insolubility have given the impression that many plastics would be free of tissue reaction. This supposed chemical inertness may, however, be misleading, since glass also is apparently inert yet able to produce marked reaction. Another factor to be considered is the addition of so called plasticisers in the process of manufacture. These chemicals and other chemicals added for coloring purposes have a tendency to "sweat out" of the plastic and may produce intense tissue reaction.¹ To further confuse, there are many different chemical formulas for commercial plastics marked under names such as lucite, plexiglass etc. Some forms have added plasticisers, others have not.

Too little attention has been paid to physical characteristics of foreign substances which may incite tissue changes. In the case of metals, the galvanic effect is capable of producing tissue necrosis.² The surface charge of foreign materials should be equally important. In addition, interfacial tension and ability to be wet by water should also be factors of considerable consequence. Gortner and Briggs,³ utilizing the method of streaming potentials, showed that there was a high electronegative charge on the surface of glass in contact with water. When the glass was coated with paraffin, which cannot be wet by water, the surface charge was zero. They postulate that absorption of positively charged colloids from serum might explain decreased clotting time in glass.

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vessels as compared to paraffin coated vessels. Similar effects may take place with instillation of supposedly inert foreign material into living tissue. Carbon particles, although chemically inert, are capable of producing fibrosis when inhaled by humans or injected into the peritoneal cavity of animals⁴. Since the carbon is chemically inactive, the fibrosis must depend upon physical factors. Such factors have received little attention in the past.

In previously described methods of study, the substance to be tested has been embedded in the tissues with subsequent observation of tissue reaction^{5, 6, 7, 8, 9}. Such methods will reveal but minimal tissue reaction since only a small surface area of the substance is exposed to the tissue. We were impressed by the methods used in testing the foreign body reaction of dusts by the United States Bureau of Mines⁴. In this method the dust, which is finely divided, and has a relatively large surface area per unit mass, is injected into the peritoneal cavity which offers a large surface area of tissue for reaction to occur. By examining the peritoneal cavity at a later date it has been possible to predict whether an inhaled dust would produce pneumoconiosis, silicosis, or no reaction. We, therefore, studied the peritoneal reaction to finely divided plastic in order to evaluate its tissue reactant capacity.

We have also studied the tissue reactions to a new plastic "Teflon,"* which is one of the most chemically inert plastics yet discovered and which has unique physical properties. The plastic is semiflexible, having bending properties somewhat analogous to lead, but it is more brittle. This plastic can easily be cut and shaped with a knife. It has a distinct waxy feel. The most unusual property of "Teflon" is that it cannot be wet with water. Nothing will adhere to it and, once formed, it cannot be cemented to any other known substance. The singular physical properties of this chemically inert plastic prompted us to study its tissue reaction along with other plastics.

MATERIALS AND METHODS

Implantations of the plastic materials were made in 21 dogs. The materials were implanted in various sites for purposes of comparison. The extent of division of the material was varied to show the effect of increasing the exposed surface area. The dogs were sacrificed at periods varying from 36 hours to six months postoperatively, at which times specimens were obtained for microscopic study. Routine aseptic surgical technic was altered only in that no gloves were used to avoid possible tissue reaction caused by the various dusting powders. The hands were carefully scrubbed and immersed in alcohol. All of the animals were given 300,000 units of penicillin in oil and beeswax postoperatively to minimize the possibility of infection and its resultant tissue responses. All plastics were placed distant to sutures. Cotton thread was used as the suture material throughout.

The materials studied in this way were FM-1 nylon, celluloid, lucite, and teflon. All materials used were free of plasticisers and color. The materials

* Furnished through the courtesy of E. I. DuPont & Co., Arlington, N. J.

were carefully washed and cleansed and copiously rinsed with distilled water. Sterilization was accomplished in an autoclave.

In an additional experiment, a suspension of extremely small particles of cellophane was made according to a method described by Cannon & Marshall for collodion.¹⁰ These washed and suspended particles pass easily through a fine gauge needle. This material was injected into the peritoneal cavity of four guinea pigs.

Although a similar type of suspension can be made with lucite, we have been unable to prepare satisfactory suspensions of nylon, polythene or teflon by chemical methods. Mechanical methods utilizing filings also fail to produce sufficiently small particles for suspensions which could be injected through a fine needle. It is possible that suspensions could be made of these materials in a colloid ball mill although we have not investigated this possibility. Lucite, celluloid and nylon were obtained in a finely divided state by taking the shavings produced by drilling holes in the solid material. Teflon was finely divided by taking small slices from a rod in fashion similar to that used for cutting paraffin sections on a microtome.

Microscopic sections were made in all cases at the time the animals were sacrificed for gross observations.

RESULTS

Celluloid—At the end of three days, an intense fibrinoplastic reaction was seen. The peritoneum was lusterless and granular. The omentum, bowel and adjacent tissues were edematous, hyperemic, and matted. The fat was indurated and friable and generally contracted. The peritoneal cavity contained small quantities of serosanguineous exudate.

The omentum was no longer discernible as a distinct structure. Microscopic sections confirmed the presence of acute inflammatory changes with infiltration of polymorphonuclear leucocytes. There was extensive edema of protein rich fluid. Protein material adsorbed on the surface of the plastic was discernible as a distinct layer. The capillaries were engorged and showed diapedesis of cells in some areas. The reaction was most intense with celluloid as compared to the other plastics.

In 70 days, the acute inflammatory reaction had subsided. Loops of bowel were bound to one another and to the omentum by dense fibrous tissue. The shrunken fibrous tissue had pulled bowel and omentum into a solid mass.

Microscopic sections taken at the 70-day interval show active fibroplasia, extending some distance from the site of plastic implantation. Epithelioid fibroblasts and giant cells were present in areas adjacent to the plastic. In some areas chronic inflammatory changes could be seen with infiltration by some polymorphonuclear leucocytes, plasma cells, large and small lymphocytes, macrophages, and Langhans giant cells. In the fissures of the solid plastic, pigment similar to hemosiderin was visible. Again the plastic material was always coated by a thin layer of protein.

Lucite—After three days the reaction to lucite was similar to that observed with celluloid but not quite as intense

Acute inflammatory changes were present which caused an extensive matting of all tissues exposed to the lucite. None of the plastic material could be found free in the peritoneal cavity. In one dog, a dilated loop of small bowel was seen entering a matted mass (Fig 1). Microscopic sections showed extensive acute inflammatory changes



FIG 1—*Photograph of the peritoneal cavity of a dog 3 days after implanting fine lucite shavings*—Omentum and bowel form a large inflammatory mass. A loop of partially obstructed and dilated small bowel, to which an Allis clamp is attached, is visible at the lower angle of the abdominal incision. At the upper angle, a Kocher clamp retracts the abdominal wall to show dense adhesions between it and the liver. An additional Kocher clamp immediately below grasps a dense adhesion which was severed. None of the leucite shavings lie free in the peritoneal cavity, all are covered by reddened inflammatory tissue.

Dogs sacrificed after the 70-day interval, showed the same dense fibrotic changes which occurred with celluloid implantation after a similar period. No marked quantitative differences could be seen either grossly or microscopically.

when compared to the late celluloid changes described above (Fig 2) It was apparent that the process had not yet become inactive

Nylon—We were somewhat amazed to find that the peritoneal reaction to finely divided nylon was identical with that described for lucite (Fig 3)

Teflon—On comparing the reactions of the above plastics to teflon very striking differences were seen Finely divided chips of teflon were seen to be

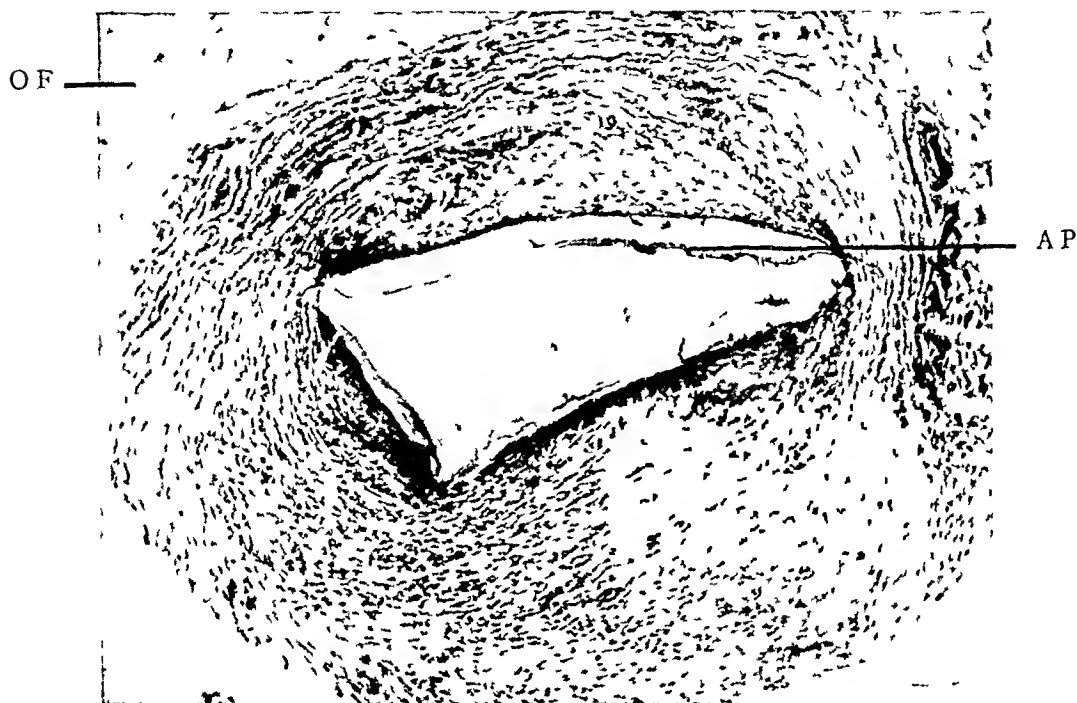


FIG 2—*Lucite shaving in peritoneal cavity* The fibrosis can be seen to extend some distance from the plastic completely replacing omental fat A thin layer of adsorbed protein (A P) is visible on the surface of the plastic

The large dark spots in some areas represent foreign body giant cells Uninvolved omental fat (O F) is present on one corner

lying free in the peritoneal cavity There were no acute inflammatory changes and no gross evidence of tissue reaction (Fig 4) Occasionally chips could be seen encased in omentum, but the extent of peritoneal reaction was certainly no more than would be expected from simple surgical manipulation

At the end of 70 days most of the chips were surrounded by omentum There was no fibroblastic reaction and the chips could be easily removed from the flimsy omental adhesions which were broken with ease

The reaction to implanted teflon is illustrated in Figs 5, 6 and 7

A thin fibrous sheath of mature fibroblasts surrounded the plastic by the end of 70 days No proliferative foreign body reaction was present

By the end of six months, the delicate fibrous capsule surrounding the plastic had not increased in thickness (Fig 6) An intact mesothelial-like layer on the omentum exposed to the plastic (Fig 7), emphasized the plastic's inability to produce tissue changes, and suggested that the fibrous capsule was



FIG 3—Photomicrograph omental tissue adjacent to Nylon for 70 days

The active fibroplasia is evident. The fat tissue has been completely replaced with fibrous tissue of varying age. At one edge is seen an area of chronic inflammation (CI). Foreign body giant cells (GC) are also seen in the tissue which was adjacent to the plastic.



FIG 4—Photograph of the peritoneal cavity of a dog 3 days after the instillation of fine microtome slices of teflon. There is no matting of bowel or omentum and the chips are seen to lie free in the peritoneal cavity. The stretched out omentum shows its thinness and the absence of even a vascular response.

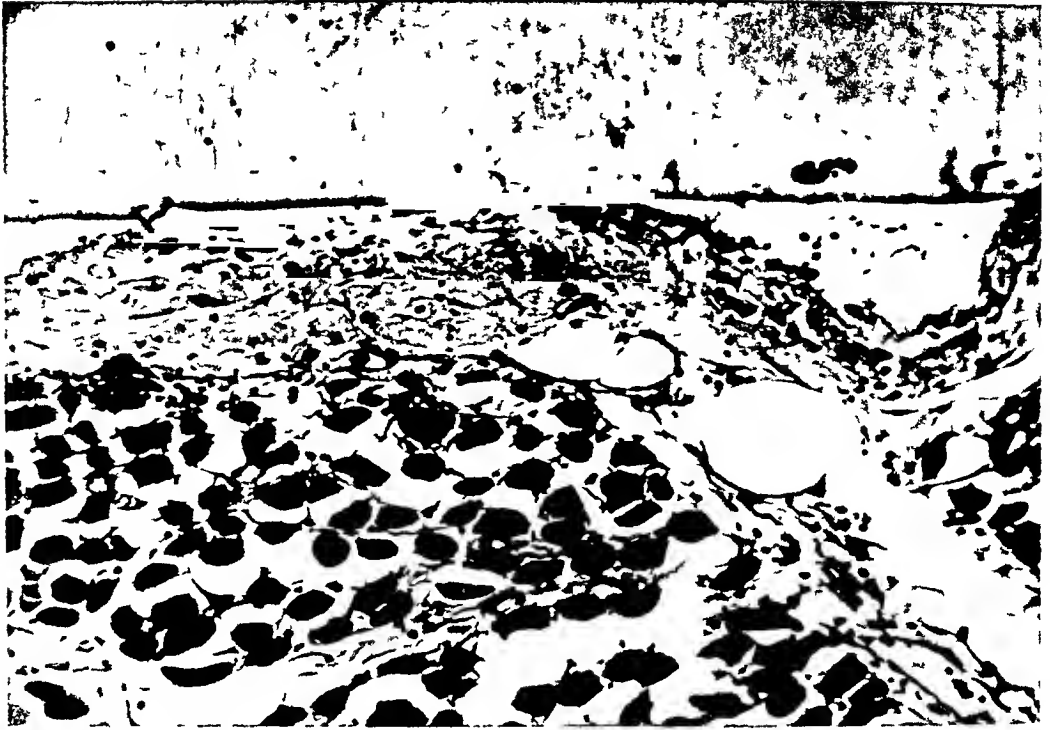


FIG 5—Photomicrograph of teflon implanted in muscle tissue 3 days after implantation—There is a somewhat cellular debris immediately adjacent to the teflon caused by surgical trauma. Observe the absence of early polymorphonuclear leukocytic response.

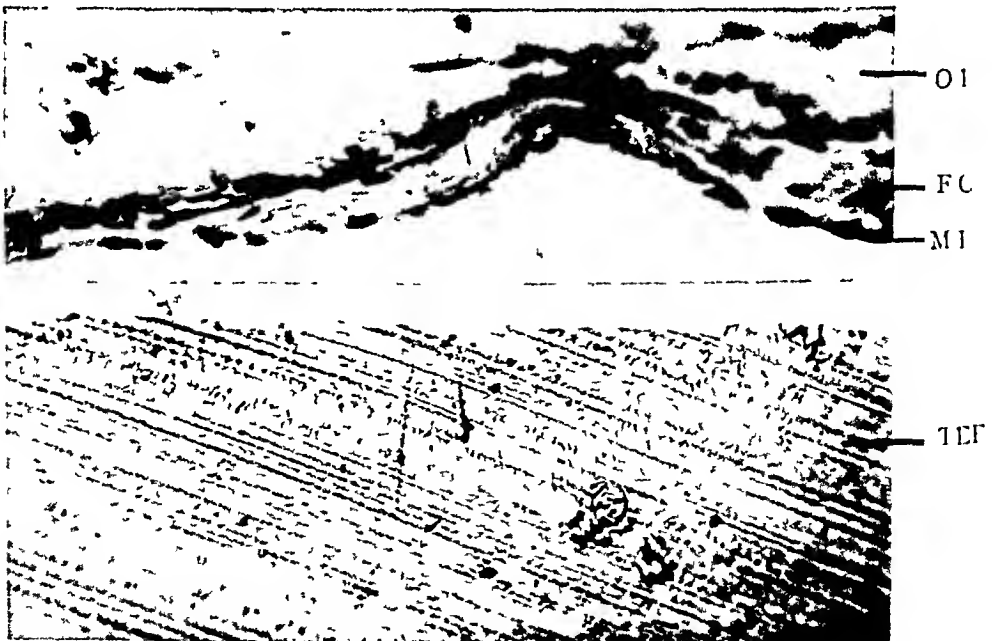


FIG 6—Photomicrograph of teflon strip in peritoneal cavity at 6 month interval.

Notice the thin layer of mature fibroblasts (FC) under the intact mesothelial layer (ML). No fibrosis is seen extending into omental fat (OF). The adjacent plastic (TEF) shows no adsorption of protein.

caused by trauma rather than by tissue reaction. In contradistinction to all the other plastics, the surface of teflon in all sections was free of adsorbed protein.

With the exception of teflon, the various plastics produced more intense reaction when finely divided material was placed in the peritoneal cavity than when tissue implantations of large pieces of material were performed. In addition, plastic implantations into tissues necessitated varying amounts of surgical trauma which was difficult to evaluate when estimating the degree of tissue response incited by the foreign material alone.

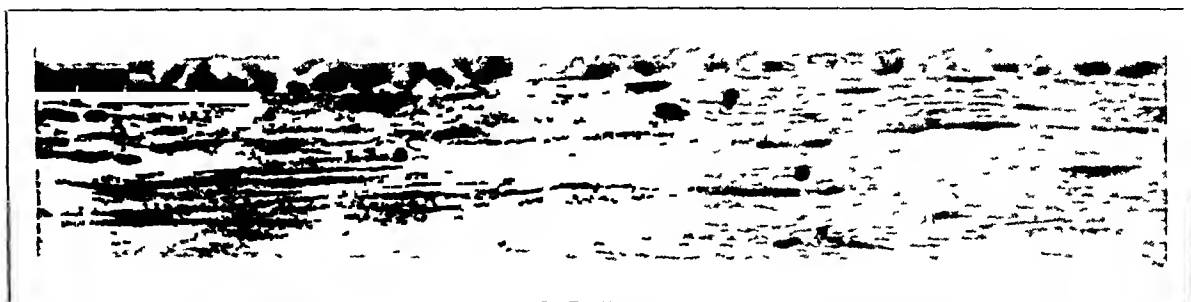


FIG 7—High power photomicrograph of omentum adjacent to plastic. Notice the intact mesothelial lining and the very thin layer of mature fibrous tissue immediately beneath it.

Cellophane—The four guinea pigs in which the suspension of cellophane was injected intraperitoneally were sacrificed 7 days, 12 days, 21 days, and 2 months following injection. A late fibrotic response comparable to that described by others was observed^{11, 12}

DISCUSSION

Nylon and lucite plastics, which have been reported as free of tissue response,^{6, 7, 13, 14, 15} are really potent exciters of tissue reaction. Previous observations are explained when one considers that but a small surface area of the plastic had been exposed to an equally small surface area of tissue. The changes therefore take place in miniature. The end result is a dense fibrous capsule surrounding the plastic. This type of reaction is seen with many non-absorbable materials.

Whether the tissue reaction is due to the dissolution of traces of the unpolymerized chemicals used in plastic manufacture or actually to the solution of an infinitesimal amount of the plastic itself cannot be determined. The authors believe that the physico-chemical characteristics of the surface of the foreign material has much to do with tissue reaction. If proteins or water are adsorbed on the surface of the plastic, the molecular configuration must necessarily be altered from that of adjacent tissue. With regard to this hypothesis, microscopic studies on all the plastics, with the exception of teflon, showed adsorption of protein on the plastic surface. All but teflon produced a proliferative foreign body reaction. Knisely has demonstrated that India ink particles injected into the blood stream are coated with a protein material before phagocytosis can occur. The adsorption of protein by plastic surfaces, which can be wetted may similarly affect the production of giant cells and proliferative foreign body reaction. Physico-chemical factors are potent stimuli in wound healing. When

the orientation of each molecule to its adjacent molecule has been restored, the proliferative reaction associated with wound healing ceases. Since metallic surfaces can also be wet with water, it would be important to restudy these substances by the intraperitoneal method.

In testing for tissue reaction to foreign material, it is essential that the greatest possible surface area of the material be exposed to the greatest possible surface area of tissue. This is best accomplished by injecting the powdered material suspended in saline into the peritoneal cavity of the experimental animal. Such a test is the most delicate indicator of tissue response. The animals should be sacrificed at the end of three days and three months to ascertain the effects. Gross observation seems sufficient. Plastics which produce tissue response when tested by this method may still be useful in surgery. However, the surface should be well polished to reduce surface area. It is certainly wiser to substitute a material which does not have these disadvantages.

Because nothing will stick to teflon, it suggests itself as an ideal substance for bile duct tubes,^{*} where formation of concretions has been a problem. Polythene, which also is somewhat water repellent, more recently has been so used.¹⁶ It should be pointed out, however, that a wide discrepancy exists in the published reports on the tissue reaction to polythene. Ingraham⁸ found polythene to be virtually a non-reactor, while Poppe²⁰ states that polythene film induced even a greater fibroblastic response than cellophane. It was the most sclerotic substance tested (Dupont & Co. was the source of the material in each case). This tissue reaction may result from dicetyl phosphate incorporated in the polythene during certain methods of manufacture.²³

Teflon should be suitable for intravenous catheters and for replacing segments of small blood vessels, since blood does not clot on materials which cannot be wet with water.¹⁷

Page and others^{11, 12} have shown that cellophane produces a marked fibroblastic response in the tissues. Cellophane can be wrapped around large vessels¹⁸ to produce gradual occlusion or to fibrose aneurysms,^{19, 20, 21} As a corollary, our work suggests that colloidal suspensions or even coarser suspensions may be injected through small needles to produce the same sclerosing effect. It, therefore, seems possible to occlude such major vessels as the abdominal aorta by injections into the surrounding adventitial tissue without the necessity of operation. Since powdered cellophane would expose the greatest possible surface to the tissue, this method seems the most logical. Caution should, however, be exercised in the clinical use of cellophane since sarcomas have been induced in a high percentage of laboratory animals by cellophane implantation.²²

It is suggested that there be a standardized method for testing tissue reaction to foreign substances. This method should have maximum sensitivity so that minor differences may be appreciated. Such a method would have the ad-

* The Zack Manufacturing Co., 1422 So. Cuyler, Berwyn, Ill., supplies many of these various appliances.

vantage of providing a base line for comparison and be sufficiently objective to offset the personal equation in interpretation

The injection of finely suspended material would be ideal. Some such suspensions can be manufactured chemically, others may be formed by the use of a colloid ball mill. If fine suspensions cannot be made, the intraperitoneal instillation of finely divided material will give adequate information.

SUMMARY AND CONCLUSIONS

The surface area of both the foreign substance and the tissue exposed are important factors in determining tissue reaction. Intraperitoneal instillation of finely divided foreign materials is therefore the testing method of choice.

Chemically inert plastics which cannot be wet with water produce the least tissue response. The tissue response to a number of plastics including a new plastic, teflon, has been described. Some practical applications evolving from these studies have been suggested.

Appreciation is expressed to Dr Eleanor Humphreys, whose many suggestions and pathologic opinions made this work possible.

Thanks is also given to Dr Alfred Angrist for his aid in the preparation of the manuscript.

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EXPERIMENTAL PULMONARY COLLAPSE*

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THE ABILITY OF CERTAIN SYNTHETIC PLASTIC MATERIALS to incite fibrosis has been described by several investigators Page¹ used cellophane to produce fibrosis of the kidney capsule Pearse² studied the effect of the same material on blood vessels Poppe and de Oliveira³ found that polyethylene produced fibrosis of the aorta in dogs Ingraham, Alexander, and Matson,⁴ reviewing the use of these materials in surgery, conclude that cellophane is irritating to tissues and that the effect of polyethylene is variable owing to differences in its manufacture for commercial purposes, pure polyethylene tubing is non-irritating These studies suggested that it might be worthwhile to investigate the fibroplastic effect of cellophane and polyethylene on the pleura and lung to determine if pulmonary fibrosis or collapse could be produced

Experiments were carried out on healthy mongrel adult male dogs weighing 3.9 to 12.7 kg Nembutal and ether were employed for anesthesia With aseptic technic pleurotomy was performed and a sheet of plastic material was wrapped about the dorsal, ventral and lateral surfaces of one lung, which was re-expanded at time of closure of the wound A total of 12 animals was used These were sacrificed three to six months after operation Autopsies were performed, findings were photographed, and sections made of tissues from treated and untreated sides

The plastic materials used were cellophane and polyethylene which were obtained in the form of sheets* Before use, the material was sterilized by immersion in 1-1,000 aqueous zephiran solution for one hour, after which it was washed in sterile physiologic saline solution

CHANGES PRODUCED BY CELLOPHANE

The changes produced by cellophane were somewhat fulminating in the two animals in which it was used There was exudation of serous fluid requiring thoracentesis—once in one animal and on numerous occasions in the other animal Both recovered, however, and were sacrificed three months after operation At autopsy, the chest wall and entire lung were collapsed toward the mid-line, the heart and mediastinum were not displaced The greatest diameter of the unoperated thoracic cavity was 6 cm, that of the operated side was 1 cm The operated thoracic cavity contained a tough fibrous mass of thickened pleura, collapsed lung, and cellophane The cellophane retained its characteristic structure and strength, it had not been

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** Cellophane, 300 PUT-71, Polyethylene, 1.5 mil polythene, sample No 4553 These were kindly furnished by Mr A S Taylor, Cellophane Division, E I DuPont de Nemours and Company

invaded by tissue. The lung of the untreated side and the heart and pericardium were normal. Sections revealed extensive fibrosis of the pleura, both parietal and visceral. The lung showed absence of air spaces, increased cellularity due to connective tissue cells, and some increased interstitial collagen formation. Because of intense early irritative reaction in response to cellophane, the remainder of the experiment was carried out with polyethylene film.

CHANGES PRODUCED BY POLYETHYLENE

This material was placed over the lung on one side in ten different animals. The early severe irritative reaction noted with cellophane was not encountered with polyethylene—the operation was tolerated well. No animals required thoracentesis, all maintained weight, were active, and appeared healthy. One animal developed a sinus from the lower end of the operative wound five months after operation (see page 87). The animals were sacrificed at intervals after operation, one group after three months and one group after six months.

Changes produced after three months. Four animals were examined for changes in the thorax three months after application of polyethylene over the lung. In one, no changes were produced, neither the lung nor thoracic cage were collapsed. The sheet of polyethylene film remained unchanged in the pleural cavity. The pleura was normal except at the region of the operative scar. In the other three animals of this group moderate degrees of collapse were produced. The thoracic wall on the treated side was pulled medially because of a capsule of thickened visceral and parietal pleura which enveloped the plastic film. The mediastinum was shifted slightly to the affected side in one animal.

Sections of treated lung from this group showed patchy increase of interstitial collagen with collapse of air spaces. Intervening spaces of lung presented a normal appearance. The pleurae were greatly thickened due to fibrosis. The plastic material had not been invaded by fibroblasts. It appeared that extensive collapse was not achieved in three months.

Changes produced after six months. The treated side of the thoracic cages of the six animals sacrificed after six months showed marked degree of collapse of the chest wall and lung (Fig. 1) comparable to that noted in the animals treated with cellophane. The plastic sheet was found to be wrinkled and in some instances bunched and to be encased in a thick fibrous envelope which had been thrown out by the parietal and visceral pleurae. The action of this fibrous envelope apparently resulted in collapse of the chest wall medially and, in turn, collapse of the lung. The mediastinum was shifted little if any to the operated side, the pericardium was in no way affected since the plastic sheet had not been placed in direct contact with it. The lung on the unoperated side was normal both grossly and histologically (Fig. 2).

Sections of collapsed lung in these animals showed uniform increase in the density of the lung tissue. The air spaces were obliterated or greatly reduced by collapse and by interstitial fibrosis. New collagen was abundant.

EXPERIMENTAL PULMONARY COLLAPSE

about the capillaries and in the alveolar walls (Fig 3) The pleura was greatly thickened

In one animal of this group, a sinus opened spontaneously in the operative wound during the fifth month Serous drainage from this sinus was apparently due to foreign body reaction since cultures of the fluid during life and at autopsy exhibited no growth The sinus, explored at autopsy, extended into



FIG 1—Collapse of the right side of the thorax and of the lung six months after application of polyethylene film about the lung The anterior part of the thickened pleura and plastic material have been removed Note loss of normal flaring curve (present on the left) on the right indicating collapse of the chest wall

an interspace and directly to a small pocket bound by thickened pleura on one side and polyethylene film on the other. No free fluid was found elsewhere. The usual degree of collapse of the chest wall and lung was produced.

In another animal an attempt was made to collapse a portion of lung by confining the application of cellophane to the upper lobe only. This was successful in collapsing the lobe and adjacent chest wall. The remainder of the pleural cavity remained free of adhesions.

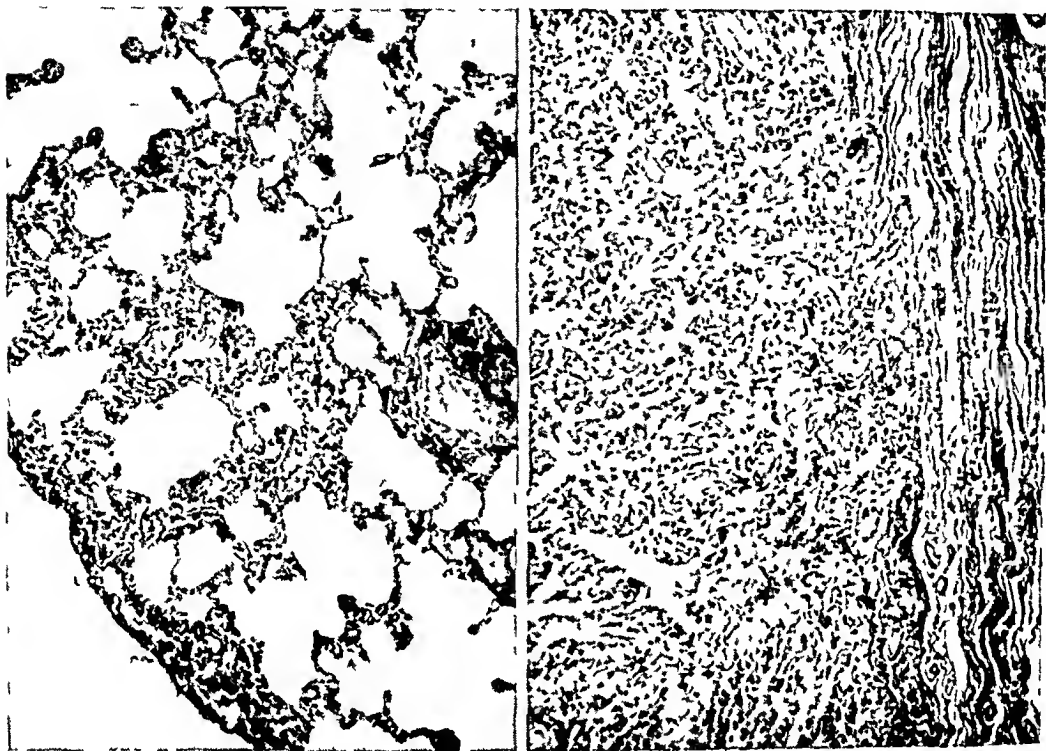


FIG 2

FIG 3

FIG 2—Section of lung from an untreated side. Van Gieson stain.

FIG 3—Collapsed lung and thickened pleura produced by polyethylene film placed over the lung. This section is taken from the junction of the lung (left four-fifths of the figure) with the visceral pleura (right fifth of the figure). Van Gieson stain.

DISCUSSION

It appears that cellophane or polyethylene film when placed over the lung in dogs will produce thickening of the pleurae and collapse of the chest wall and lung, some fibrosis of the lung follows. Polyethylene of the type studied seems to be as effective as cellophane and is free from fulminating pleural reaction produced by the latter substance. In one instance a late reaction to the plastic material resulted in an open sinus through the operative scar, but without detectable infection. The changes produced are compatible with life and health in dogs. Although comparative measurements of respiratory function were not made, it was observed that operated animals were as active as normal and exhibited no evidence of dyspnea.

One difficulty in further application of "cellophane fibrosis" to produce

pulmonary collapse arises from the variability of plastic films with respect to ability to induce fibrosis. The fibrous reaction is apparently produced by plasticizers used in manufacture of the product for commercial purposes. The film, for medical purposes at least, is a convenient vehicle for maintenance of an irritating chemical in a certain location. More recently, Blakemore⁵ has indicated that polyethylene film of known fibroplastic qualities can be obtained.

Whether or not cellophane collapse of the lung would be applicable to collapse therapy of human tuberculosis is conjectural. The reaction of the pleura of a tuberculous lung might well be quite different from the reaction of healthy dog pleura. On the other hand it is quite likely that if the production of localized thickened pleura and adhesions should be desirable, as in obliteration of an emphysematous bleb, either cellophane or polyethylene of suitable composition would be quite effective.

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STREPTOMYCIN IN SURGICAL INFECTIONS VII
NONPULMONARY TUBERCULOSIS
(LYMPH NODES, URINARY TRACT, BONE, AND PERITONEUM)*

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THIS COMMUNICATION reports United States Army Hospital experiences with streptomycin therapy in 35 cases of tuberculous lymphadenitis 46 cases of infection of the genito-urinary tract, 24 cases of tuberculosis of bone and 16 cases of ulcerative tuberculous enteritis

TUBERCULOUS LYMPHADENITIS

Up to June 1, 1948, 35 cases of tuberculosis originating in the lymph nodes had been treated with streptomycin and fully studied in U S Army hospitals as part of the Army streptomycin program

Previous Government Experience In Government hospitals, 36 patients with lymphadenitis of proved tuberculous origin were treated with streptomycin prior to March, 1948. In 12 patients glands disappeared, in 18 they became smaller and in six they were unchanged in size. In addition to these cases, 51 patients with draining lymph nodes were treated and studied. Forty-five of the 51 were regarded improved, but the Committee could not state whether the lesions in these 45 disappeared or merely became smaller. The Committee regards streptomycin as of value in tuberculous lymphadenitis.

Army Experience The age range in the 35 patients with tuberculous lymphadenitis in the Army series was from 18 to 52 years. The majority were in their early twenties. Fourteen patients had tuberculosis in other areas of the body, chiefly the lungs. In two cases the disease had spread to other parts of the body in addition to the lungs and the lymph nodes. In 26 cases the lymphadenitis was located in the anterior and posterior cervical chain. In four cases the axillary nodes were involved and in five the mediastinal nodes. In 16 cases the lesions had progressed to necrosis with sinus-formation and were discharging pus. In the remaining 19 cases the lymph nodes were enlarged but still intact. Diagnosis was by biopsy supplemented in a few cases by cultures or by guinea pig inoculations.

The dosage schedule in most cases was 15 to 20 Gm of streptomycin daily by the intramuscular route, given in three or five injections, in a few instances the dose was 1 Gm a day given in two injections. The duration of

* Submitted May 10 1948

treatment ranged from 10 to 120 days, most of the patients were treated for periods of 10 weeks. Adjuvant local measures were employed in four cases.

Streptomycin therapy was used with two objectives in this series of cases. The first objective, in 26 cases, was to arrest the infection by the administration of the drug. In the other nine cases streptomycin was used before operation, to prepare the patient for surgery and to protect him against dissemination of the disease, and after operation, to lessen the danger of sinus-formation and metastases. In this group of cases the average period of administration was 56 days. Six of the 19 patients with simple lymphadenitis were treated by surgical measures, which were also employed in three of the 16 cases in which sinus-formation had occurred.

Uncomplicated Tuberculous Lymphadenitis Thirteen cases of lymphadenitis without sinus-formation were treated only by streptomycin, with good results in nine cases and failure in four. One of the patients who had no results from streptomycin also had syphilis, for which he had been treated with penicillin for three weeks; the associated syphilitic infection perhaps played a part in the failure of the lymph nodes to regress. The other patient who had no results from streptomycin therapy had had scrofula for 18 years, and the disease was probably so far advanced that extensive fibrotic changes had resulted. Whatever the reason, there was no demonstrable change in the state of the lymph nodes at the end of 60 days of streptomycin therapy. The third failure was in a patient with widely disseminated miliary tuberculosis, and the last failure was in a patient with cervical lymphadenitis and minimal pulmonary tuberculosis in whom there was no regression after two months' treatment.

Six patients with uncomplicated lymphadenitis were treated with streptomycin in combination with surgical measures. In four cases the drug was used for 12 days, after surgical excision of tuberculous cervical lymph nodes, as a prophylactic measure to ensure primary wound healing. In the other two cases the patients were submitted to exploratory thoracotomy and biopsy of the mediastinal lymph nodes, and received streptomycin for 30 days, to protect against spread of the disease, poor wound healing and other complications. There was uncomplicated healing without spread of the disease in five patients and no change in one patient.

Tuberculous Lymphadenitis with Sinus Formation There were 16 patients in this group, three treated with surgery and 13 without surgery. One of the three patients treated by surgical measures in this group had an "orange size" tuberculous abscess of the axilla; acid fast bacilli were recovered from the exudate. Streptomycin was given by the intramuscular route for 18 days before and 81 days after surgical drainage of the abscess, and the wound was dressed every other day with gauze impregnated with 1 Gm. of streptomycin dissolved in saline. The amount of exudate slowly decreased and the wound appeared well healed six weeks postoperatively. There has been no sign of recurrence in a six months' follow-up. The second patient treated by surgery was submitted to six weeks of streptomycin therapy for draining sinuses in the

neck originating in caseating, matted anterior cervical lymph nodes. The adenitis did not resolve. Drainage lessened but continued. Excision of the involved glands *en bloc* with the sinus tracts and surrounding skin was then performed. The wound healed solidly. Streptomycin was continued for three weeks postoperatively. There has been no recurrence in a four-months follow-up period. The third patient had a draining axillary sinus following incision three years previously. The tract and compromised tissue were excised and 1 Gm. of streptomycin instilled. The antibiotic was administered intramuscularly for 14 days postoperatively. The wound healed and has remained so.

In 11 of the 13 patients with tuberculous lymphadenitis complicated by sinus formation who were treated by streptomycin without surgery, the results were good. The sinuses healed during the course of therapy and there was impressive regression in the size of the lymph nodes, which in some instances disappeared so completely that they were no longer palpable. The remaining two cases in this group were therapeutic failures. The first patient who had no results from streptomycin therapy had miliary tuberculosis with draining cervical lymphadenitis. Death occurred after 115 days of therapy. Culture sensitivity tests shortly before death revealed extreme resistance to streptomycin of the organisms. In the second unsuccessful case streptomycin was given for 10 days, during which period the draining tuberculous sinuses closed. Streptomycin was not continued, however, because of the appearance of generalized purpura. It was realized that this development might be the result of a long previous course of salicylate therapy, but the possible responsibility of streptomycin could not be discounted. Three weeks after the interruption of therapy the sinuses re-formed and the amount and character of the drainage became essentially the same as before streptomycin had been given.

Comment The follow-ups in the Army series of cases of streptomycin-treated tuberculous lymphadenitis are too short to permit generalizations as to the value of this antibiotic in this condition. Tuberculous lymphadenitis, however, is a notoriously obstinate condition, and the excellent results obtained in many cases (20 of the unoperated cases, and six of the operated cases in the series) suggests the propriety of the continued use of streptomycin in its management. Noteworthy is the fact that one failure could be attributed to streptomycin fastness of the organism and the other to streptomycin toxicity.

The results of streptomycin therapy were generally better and prompter when surgical measures were combined with it. Apparently the preoperative and postoperative use of this agent is helpful in preventing sinus-formation and in expediting the closure of sinuses which exist. The ideal treatment would seem to be saturation of the tissues by the administration of streptomycin at therapeutic levels for a period of one to two months. If at the end of that time there is no clinical response and if the case is amenable to surgery, block dissection of the lymph nodes or removal of the primary focus of infection should be considered. Following surgery, the same therapeutic levels should be maintained until it is clear that primary healing has been accomplished. Packing the operative site with gauze saturated with a solution of streptomycin

was carried out in only three cases in this series, but would seem desirable as a means of shortening the period of disability. Moreover, cases which had been refractory to streptomycin before removal of the infected tissues might show improvement under this treatment after the local blood supply had become adequate.

Good results cannot be expected in tuberculous lymphadenitis unless the course of streptomycin therapy is adequate. Long courses of therapy may, however, give rise to toxic reactions and the patient should be carefully watched. (The use of dihydrostreptomycin may reduce the severity and incidence of neurotoxicity.)

It was of interest in the Army series, when the same patient presented multiple involvement, that there was no apparent correlation between improvement in the local lymphadenitis and changes in pulmonary tuberculosis processes. Even in cases in which tuberculous lymphadenitis was apparently cured, roentgenograms evidenced no perceptible changes in the pulmonary disease.

TUBERCULOSIS OF THE GENITO-URINARY TRACT

Up to June 1, 1948, 46 fully studied cases of tuberculosis of various portions of the genito-urinary tract had been treated with streptomycin in U. S. Army hospitals as part of the Army streptomycin program.

Previous Government Experience. Up to May 1, 1947, streptomycin had been administered in 41 cases of proven genito-urinary tuberculosis in hospitals of the Army, Navy, and Veterans Administration. Thirteen of this group had 120 days of treatment and had multiple lesions of the genito-urinary tract, on an average of 3.5 lesions per patient. Cultures of vesical urine were made every fortnight and cultures of ureteral urine every 40 days during therapy. Nine of the 13 patients improved, but, in most cases, only temporarily as to frequency and dysuria. Vesical capacity increased in 10 of the 13. Cystitis diminished in 11 cases. Twenty-five of 32 lesions in the posterior urethra, prostate, and seminal vesicles improved. Only four of the 13 patients continued to have positive urine cultures after the first 40 days of treatment, and only two of these were positive one month after the conclusion of treatment. In both instances the bacilli were resistant to more than 500 micrograms of streptomycin per cubic centimeter. On the other hand, there was little change in the excretory or retrograde urograms.

It was the opinion of the joint committee that while these results seemed hopeful, only time could tell whether improvement in the lesions of the lower urinary tract would be permanent. The lack of change in the urograms should be noted. In a more recent report the Committee is more optimistic regarding the favorable effects of streptomycin in genito-urinary tuberculosis.

Army Experience. The 46 cases of proven genito-urinary tuberculosis observed in the Army streptomycin program were men of military age. In 18 cases there were tuberculous lesions elsewhere in the body, generally in the lungs. The course of treatment was adapted to the case. At the conclusion of treatment 11 patients were regarded as benefited and 11 as not benefited, while in 24 cases the results were too equivocal to permit any conclusions as to the value of streptomycin in tuberculosis of the genito-urinary tract.

Improved Group Four of the 11 patients who were regarded as improved at the end of treatment had tuberculosis apparently confined to the bladder and seven others had tuberculosis of the bladder and kidneys, three patients in the latter group also had tuberculosis epididymitis

Only one of four patients whose tuberculous lesions were confined to the bladder had pulmonary tuberculosis, it was declared inactive. All were given 2 Gm of streptomycin intramuscularly daily in five doses, over a period of 60 to 80 days. These patients had nephrectomies for tuberculosis prior to streptomycin therapy, with persistent draining sinuses in one. Cystoscopies showed multiple ulcerations of the vesical mucosa. In all patients relief from frequency and dysuria occurred progressively after two weeks of streptomycin therapy and vesical capacity increased significantly. Cystoscopy revealed progressive healing of the vesical lesions. The draining sinus after nephrectomy, present in one patient, closed during streptomycin treatment and remained healed. Other signs of improvement were negative smears and cultures and patients were observed for six months after the conclusion of treatment. There was a return toward normal limits of erythrocyte sedimentation rates. There was no clinical or bacteriologic evidence of relapse. Three of the four patients showed a significant gain in weight.

The six patients with vesical involvement and other lesions in one or both kidneys, who were regarded as improved, received streptomycin for an average of 120 days by the above dosage. A 31-year-old male with right renal and vesical tuberculosis showed symptomatic and cystoscopic evidence of improvement of vesical tuberculosis. Retrograde urograms, however, showed no improvement of the right kidney after 12 weeks of therapy, and the cultures were positive for acid fast bacilli resistant to streptomycin. Therefore, a right nephrectomy was performed. Examination of the kidney showed no change which could be attributed to streptomycin. The wound healed primarily. Streptomycin was discontinued six weeks postoperatively. The patient's condition at present is good. Each of the six patients had a similar clinical course, cystitis and dysuria were improved, the ulcerated lesions in the vesical mucosa disappeared, and urines became negative for acid-fast bacilli. There was, however, no change in the radiographic appearance of the kidney. Three patients had tuberculosis involving the bladder, ureter, one kidney, testicle and epididymis. Streptomycin was given two weeks before and six weeks following removal of the involved kidney, ureter, testicle and epididymis. In all instances the therapy appeared beneficial. The wounds and scrotal sinuses healed primarily and the cystitis cleared. Several cultures of the urine were negative for acid-fast bacilli, during the follow-up period.

Doubtful Group The 24 patients with genito-urinary tuberculosis who had doubtful results from streptomycin fell into three classes. Four patients submitted to epididymectomy and/or orchiectomy for tuberculous epididymitis and/or orchitis received streptomycin postoperatively in daily dosages of 2 Gm. The wounds healed primarily in three out of the four cases. Six patients with unilateral tuberculosis of the kidney were treated before and

after nephrectomy. The wounds healed primarily and the cystitis subsided. In the six cases followed there was no breakdown of wounds during a four-month period of observation, and no evidence of spread of the disease by the operation. The 14 doubtful cases of the third class received no genito-urinary surgical therapy. These cases had both kidneys involved, tuberculosis of a remaining kidney, or scrotal and testicular tuberculosis.

Unimproved Group Of the 11 patients which were not benefited, nine received 1 Gm or less of streptomycin per 24 hours, one had pulmonary tuberculosis, and one had tuberculous epididymitis.

Comment This series of cases of tuberculosis of the genito-urinary tract is too small to be of any statistical significance. The fact, however, that only 11 of 46 patients improved on streptomycin therapy is not promising. It is probably important that most of the patients in whom improvement was observed had tuberculosis of the bladder or a scrotal sinus and that, in those in which other organs of the genito-urinary tract were involved, improvement was confined to the bladder or scrotum, the disease in the other organs showing practically no alteration. This suggests that streptomycin may be useful in the preoperative and postoperative management of cases of genital tuberculosis in which excision of the focus is undertaken. Per primam healing in tuberculous subjects is not readily achieved but was accomplished in a number of cases in this series under streptomycin protection.

The value of our data is diminished by an inadequate follow-up period and by the fact that removal of a tuberculous kidney will often, in itself, diminish a tuberculous cystitis. It appears that streptomycin without nephrectomy has not been given an adequate trial in unilateral tuberculous nephritis. Improvement has followed use of streptomycin for bilateral tuberculous nephritis and tuberculous cystitis.

The following are considerations for the use of streptomycin in tuberculosis of the genito-urinary system.

- 1 To be given prophylactically before, during, and after operations on infected organs to prevent wound-infection,
- 2 To be given for a draining tuberculous sinus, assuming that the main focus of infection has been resected,
- 3 To be given for tuberculous cystitis,
- 4 When the renal infection is accompanied by moderate pulmonary tuberculosis the genito-urinary infection is especially resistant to streptomycin,
- 5 The dose of streptomycin should not be less than 2 Gm q d (as 0.5 Gm q 6 h).

TUBERCULOSIS OF BONE

Up to June 1, 1948, 24 patients with tuberculosis of various bones (18 of the spine, six of the extremities) had been treated with streptomycin in Army general hospitals.

As of April, 1948, 192 patients with tuberculosis of various bones, including the vertebrae, were under treatment with streptomycin in Government

hospitals. The results showed a slow but appreciable improvement in a majority of the tuberculous lesions of bone and joints.

In 20 of the 24 patients treated with streptomycin in the Army program culture, tissue sections, or both, revealed *Mycobacterium tuberculosis* as the etiologic agent. In the remaining four cases, there was clinical and roentgenologic evidence of the disease. The patients, who ranged in age from 18 to 38 years, were chiefly young men who were on active duty or who had just been separated from service when the disease was first noted. Fifteen of the 24 were white, seven were Negroes and two were yellow.

Eleven patients, eight with tuberculosis of the spine and three with tuberculosis of bones of the extremities, had pulmonary lesions, chiefly inactive, at the time of treatment. Two patients with tuberculosis of the spine also had tuberculosis of bones of the wrist and hand, respectively, and another had tuberculosis of the knee joint with sinus formation. One patient with tuberculosis of the elbow had an active tuberculous peritonitis. Soft tissue lesions were associated with the bone lesions in all cases. The average duration of illness before therapy was 14 months.

Six of the 24 cases showed some improvement in the status of the bone lesion after streptomycin therapy. Seventeen bony lesions were unchanged roentgenologically and one showed progressive destruction while on the antibiotic regimen. Eighteen associated soft tissue lesions were markedly improved, three were questionable and two were unaffected.

The results seemed to bear some relation to the status of the patient at the time treatment was begun. In chronically ill patients the average time for response to therapy was 69 days. In patients with subacute disease it was 51 days and in patients in good condition it was 37 days. One patient in excellent condition at the beginning of treatment showed no response at all to therapy and two patients, both chronically ill, developed tuberculous abscesses while under treatment.

Tuberculosis of the Spine. The 17 patients with tuberculosis of the spine (Pott's disease) had involvement of a single vertebra in one case, of two vertebrae in 11 cases, of three vertebrae in three cases, of six vertebrae in one case, and of seven vertebrae in one case. In four instances there were other distinct manifestations of tuberculosis of the bone. Fifteen of the 17 patients had adjacent paravertebral abscesses and four had other cold abscesses in distant locations.

Thirteen patients received streptomycin 2.0 Gm. daily for periods ranging from 38 to 140 days, four of these were treated 120 to 140 days. Two cases received 1.0 Gm. for 120 days and the remaining two cases were given 2.4 Gm. for 49 days and 3.0 Gm. for 91 days, respectively. In all instances streptomycin therapy was carried out in association with such standard measures as bed rest, the application of casts, blood transfusions, heliotherapy, and high-vitamin, high-caloric diets. Aspiration of the lesion was carried out in ten cases, incision and drainage in seven cases, spinal fusion in seven cases.

sequestrectomy in two cases and lobectomies including a right pneumonectomy in two cases

Results The response to streptomycin therapy in 17 cases of Pott's disease was regarded as good in three, fair in 11, and poor in three. The good results included arrest of the disease process in the bone with signs of recalcification by roentgen-ray, loss of pain and increase in the range of motion of the involved joints, early healing of the longstanding soft tissue lesions and marked improvement in the general well-being of the patient.

The responses to drug therapy listed as fair in the cases analyzed manifested roentgenologic evidence of no further progress in the disease of the bone, a successful fusion, rapid healing of the soft tissues which averaged 16 days and an improvement in the general condition of the patient.

The three cases listed as poor results showed roentgenological evidence of progressive bony destruction with little or no tendency for the soft tissue lesions to heal during the 120 days of treatment.

The seven spinal fusions carried out in this series of patients were all eventually successful. In the four cases in which fusion was carried out in the third or the fourth month, of streptomycin therapy, the postoperative course was uneventful. In three cases in which fusion was carried out without such protection, the postoperative course was stormy and wound dehiscence with infection occurred in one case.

Tuberculosis of the Bones of the Extremities Of the six patients treated with streptomycin for tuberculosis of the extremities two had lesions in the metatarsals, two the metacarpals with a second lesion in the tibia of one, in the remaining two patients involvement of the elbow joint and scapula respectively were present.

Five of the patients received 2.0 Gm. of streptomycin daily for an average of 90 days. One patient was administered 1.0 Gm. for 104 days. One case received in conjunction with his intramuscular course, local irrigation of a sinus tract with 1.0 Gm. daily for 205 days. Sensitivity to the drug was noted in all the patients on 2.0 Gm. daily doses. Manifestations were mild vertigo, headache, and cutaneous rash. In all instances accepted supportive measures were utilized. Sequestrectomy was performed in four instances, repeated aspiration in one and the local excision of tuberculous tissue in another.

Results The response to streptomycin therapy in six tuberculous lesions of the extremities was regarded as good in three cases and fair in the remaining three.

The improved cases demonstrated arrest of the destructive process and the recalcification of the bone as seen by roentgenologic survey after 60 days of therapy. Soft tissue lesions healed during the first month of therapy. The cases graded as fair demonstrated no further bone destruction but no regeneration was noted. Soft tissue sinuses and abscesses healed within 35 days after the initiation of therapy. The motion of the joints involved increased in range and pain on motion disappeared. The general condition of the patient was improved.

Local irrigation of the sinus tract in one case was unsuccessful and surgical excision of the tract was required for closure of the lesion

Sequestrectomy performed without the protection of streptomycin was unsuccessful. When performed in conjunction with the drug successful closure with grafted skin was obtained

COMMENT

The results of streptomycin therapy in this small series of cases could not possibly be regarded as definitive though certain conclusions seem warranted. There is no doubt that this drug can influence favorably the equilibrium between soft tissue defenses and sinus tract formations. On the other hand, the fact that abscesses, unless they are aspirated or drained, show resistance to dissolution is no more unexpected in abscesses of tuberculous origin than in those of coccal origin. The fact that two patients in the series, while under treatment, showed improvement in the status of the bone may be merely coincidental but also raises the hope that follow-up observations may show bone response in other cases in which it was not immediately evident, or that larger doses of streptomycin may produce better results in this respect.

This series demonstrates again that streptomycin is a useful umbrella for the surgery of tuberculous lesions. Surgery had to be resorted to in numerous cases in this series, for the usual reasons, and osteomyelitis of the long bones with sequestra remains a surgical problem, but the use of streptomycin before and after operation seems to prevent complications and promote wound healing.

TUBERCULOUS PERITONITIS (ULCERATIVE TUBERCULOUS ENTERITIS)

Up to June 1, 1948, 16 patients with tuberculous peritonitis (ulcerative tuberculous enteritis) and one patient with non-specific mesenteric granuloma had been treated with streptomycin and fully studied in Army general hospitals.

Previous Government Experience The previous experience with streptomycin-treated peritonitis in Government hospitals was with 27 cases, in 19 of whom good results were secured by the intramuscular administration of the drug, with complete relief of symptoms and disappearance of ascitic fluid whenever it was present. The conclusion was that, although the series was small, the definite and uniform good results obtained by this mode of treatment in respect to symptoms warrants continued use of streptomycin, and furthermore that the value of oral administration of streptomycin is worthy of investigation. It was noted that in the presence of continuing pulmonary infection the permanence of the effects of streptomycin on lesions of the alimentary tract were suspect, though this consideration in no wise lessened the usefulness of the drug for relief of symptoms.

Army Experience Of the 17 cases of tuberculous peritonitis treated with streptomycin in Army hospitals, the diagnosis was confirmed in ten by positive cultures of tissue sections for acid fast bacilli. In six cases the diagnosis was made on the basis of the history, the clinical course, and laparotomy. In one case the history, clinical course, and findings at operation suggested tubercu-

lous peritonitis, but the diagnosis was not substantiated by culture or inoculation, and tissue sections of mesenteric lymph nodes showed epithelioid giant cell granuloma

All patients but two, who were young females, were young men of military age. Practically all were described as undernourished, chronically or acutely ill, and progressively going down hill. All were extremely ill at the time streptomycin treatment was instituted. In 16 cases the duration of symptoms varied from 36 days to 16 months, in the 10th case the patient had been acutely ill only three days but a history of chronic illness of six years duration was obtained.

The dosage of streptomycin varied from 1.5 to 4.7 Gm daily, administered in divided doses by the intramuscular route. Five of the 17 patients received 1.0 Gm daily, 10 received 2.0 Gm, and two others from 2.5 Gm and 4.7 Gm daily. The duration of treatment extended from eight to 28 days in five patients, 60 days in five patients and from 90 to 120 days in seven patients. Five patients also received penicillin. Duration of therapy with various dosages has not exhibited any significant correlation with improvement in the treatment of this disease.

Streptomycin therapy was accompanied by the usual sanatorium supportive measures. Intestinal decompression was used on both prophylactic and therapeutic indications in a few cases. Laparotomy was carried out in 14 cases.

Results Eleven of the 16 patients who had proven tuberculous peritonitis were regarded as markedly improved, three were regarded as slightly improved and three were unimproved. Results were determined chiefly on the basis of whether or not they could reasonably be attributed to the use of streptomycin. A patient was regarded as improved by the course of therapy if, following the administration of the drug, there was an early reversal of the downhill course, and if the convalescence was of a character which would not have been anticipated in the light of the disease process.

Improved Group In the 11 patients of streptomycin-treated tuberculous peritonitis in which improvement was evident, the pattern in all was somewhat similar. The response to therapy was rapid in four patients, in one of which improvement was evident on the third day of treatment. In the majority of cases, however, the improvement occurred gradually over a period of 28 days. A fall in temperature occurred as early as the first three or four days of treatment, followed by symptomatic relief from abdominal cramps and pain, decrease in abdominal distention, a change in facies, and improvement in appetite. The fall in the sedimentation rate was less prompt.

The patients first ceased to lose weight and then began slowly to gain as appetite improved. The doughy consistency of the abdomen and the intra-abdominal masses resolved slowly, in two cases only after 90 days of therapy.

Ten of the 11 patients were subjected to laparotomy. Eight received streptomycin in 2.0 Gm daily dosages immediately after operation and all had uncomplicated recoveries. The ninth patient, who had been submitted to entero-enterostomy for intestinal obstruction, was given 8.0 Gm of strepto-

mycin daily by the intramuscular route, combined with penicillin, for 72 hours and then received 4.0 Gm daily for the next 10 days. His postoperative course was febrile. Thereafter varied dosages of streptomycin were given but there seemed no definite correlation between the dosages of the drug and the febrile reaction. The temperature finally dropped to normal on the 22d postoperative day, after therapy was discontinued. Streptomycin might have been responsible since it was given in unusually large dosage. The remaining patient subjected to surgery did not receive streptomycin after operation, and three draining sinuses appeared in the operative wound. All had healed spontaneously before the patient was given streptomycin five months later for improvement of his general condition.

One case in the improved group is worthy of special mention. A 20-year-old woman was admitted with a history of chills, temperature elevations to 102°F, nausea, and vomiting. Abdominal symptoms and signs of pain, tenderness and distention gradually increased over a period of five weeks prior to admission. Penicillin and sulfadiazine were without effect, and pleural effusion developed while they were being given. The patient was in extremely serious condition. Streptomycin was given, 1.5 Gm daily for 12 days, 3.0 Gm daily for the next 11 days, then 1.5 Gm for another four days. At this time the drug was discontinued because of complaints of headache, nausea, dizziness and clouded vision. Three days after streptomycin therapy had been instituted, however, the temperature returned to normal limits, abdominal pain was less acute, and nausea and vomiting ceased. There was a weight gain of eight pounds while on therapy. Two weeks following the cessation of streptomycin patient was allowed to go home.

Questionable The three patients considered to have a questionable response to streptomycin had in common symptomatic relief of abdominal pain, nausea and vomiting, and a slight but inconstant increase in appetite and weight. They are listed as doubtfully benefited because of a diminished yet persisting intra-abdominal mass and a doughy consistency of the abdomen after 120 days therapy.

Unimproved Of the three patients considered unimproved two died. The third, not definitely diagnosed as tuberculosis, showed no improvement. The first failure, a 34-year-old white male with active pulmonary lesions and a widespread peritoneal involvement progressed rapidly downhill in the face of 120 days of streptomycin and a total dosage of 240 Gm. Oral streptomycin, 1.0 Gm daily, seemed to relieve the nausea and diarrhea during the month just prior to death.

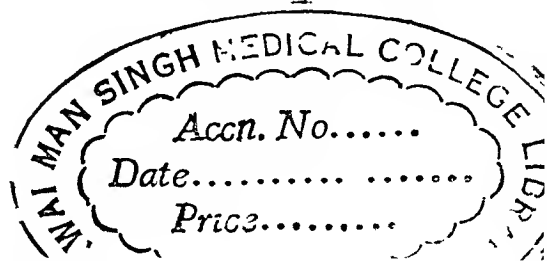
The second failure was in a 24-year-old white male with a 13-month history of constipation and a "swelling" of the right lower quadrant of the abdomen. A pleural effusion was demonstrable. Laparotomy revealed plastic tuberculous peritonitis. Numerous episodes of intestinal obstruction were relieved by decompression with the Miller Abbott tube. Malnutrition with progressive secondary anemia were present and repeated blood transfusions were necessary. Streptomycin was started, 4.0 Gm daily intramuscularly.

together with penicillin in daily dosages of 240,000 units. At the end of four days the temperature fell to normal limits, but there was no improvement in the clinical course and death occurred after 16 days of streptomycin. Post-mortem examination revealed stenosis of the ileum with obstruction from plastic tuberculous adhesions. Streptomycin in this case was frankly a measure of desperation. No significant results were anticipated from its use and none were secured.

The third poor result was in a 28-year-old man who had become ill 12 months before he was treated with streptomycin. Shortly after the onset of symptoms (March, 1946) laparotomy was performed for intestinal obstruction complicated by peritonitis. Sinuses developed in the wound postoperatively and drained intermittently. Eight months after the first operation the abdomen was again opened to determine the character of a mass palpable beneath the sinus tracts. Exploration revealed an abscess communicating with the sinuses as well as partial intestinal obstruction from a plastic peritonitis. Coliform bacteria were cultured from the abscess. Entero-enterostomy was performed. Following this operation the patient had a number of febrile episodes and during May and June 1947, he received two courses of streptomycin, and five courses of penicillin. During the first course of streptomycin 11 Gm were given over a 13-day period and during the second course 16 Gm were given over an eight-day period, without any response. On July 1, 1947, elective laparotomy revealed an abscess in caseating nodes. All infected tissues were excised. Slight symptomatic improvement followed the administration of 20 Gm of streptomycin daily for 25 days. The sedimentation rate and leukocyte count remained elevated and there was no gain in weight. Culture of the exudate from the abscess and the lymph nodes excised at the last operation revealed no acid-fast bacilli. Tissue section of the lymph nodes was reported as showing epithelioid cells, giant cells and necrotic debris but no tubercles, fungi or acid fast bacilli. The tuberculin test was positive only at 1:100 old tuberculin. The final diagnosis was nonspecific granuloma. This case emphasizes the need for accurate diagnosis if beneficial effects of streptomycin therapy are to be expected.

COMMENT

The 16 of 17 patients in this series with proved tuberculous peritonitis were all extremely ill when streptomycin therapy was begun. After therapy 11 were markedly improved, four were slightly benefited, and three were unimproved. Two patients died. The series is small, but the results suggest that streptomycin is the drug of choice for the treatment of tuberculous peritonitis. There is no justification, however, for claiming that these patients were cured. The follow-up data are meager. Adults may present remission or arrestation of tuberculous peritoneal processes in the absence of specific therapy and later may present exacerbations of the disease or may die of tuberculous lesions elsewhere. It remains, therefore, for larger groups of tuberculosis of the peritoneum to be treated by streptomycin and to be fol-



lowed for periods of years before any conclusions as to the value of this agent for this condition can be defined For the present time 15 Gm streptomycin daily for 60 days would appear to be optimum treatment

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SURGICAL REPAIR OF LACERATIONS AND FISTULAS OF THE PAROTID DUCT*

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RESULTS FOLLOWING SURGICAL REPAIR of laceration or fistula of the parotid duct so far have not been uniformly satisfactory. This has been true especially of attempts at repair in the more chronic types of fistula. The problem is one that may suddenly confront any surgeon even though injury of the parotid duct occurs infrequently.

The authors have treated surgically five patients with lacerated parotid duct, in some cases the condition having been present for a few hours, in others a few weeks. In each case successful results were obtained by the use of a simple technic that will be described. No claim of originality is made since the main principles of the operation already have been applied by others.

ANATOMY

The parotid duct leaves the anterior border of the parotid gland and extends forward horizontally across the masseter muscle. It is accompanied by branches of the facial nerve and facial artery which usually are to be found running above the duct. The duct passes inward at the anterior border of the masseter muscle, piercing the layer of fat and the buccinator muscle. It then passes forward for about 5 mm, to emerge through a narrow opening in the papilla opposite the second upper molar tooth. The course of the duct will be roughly shown by drawing a line from the lower edge of the external auditory meatus to the upper border of the upper lip.

The duct is a fibrous tube about 6 cm in length and 4 to 5 mm in diameter. It ejects saliva during mastication by action of the contractile tissue in its walls. At the papillary end of the duct there is a sharp angulation that acts as a valve, preventing food from entering.

HISTORY

Prior to 1926 there were few reported cases in which anastomosis of the parotid duct was made. Schmieden,¹ in 1916, reported such a case but gave no description of the technic used. Since 1926 there have been occasional reports of duct repair but in each instance the series of cases has been too small to allow any definite conclusions regarding the method used. In reviewing the various technics described it is evident that the use of a dowel to splint the duct has been generally accepted. Tees,² in 1926, reported two cases in which a strand of catgut was used to serve as a dowel over which the duct was approximated by means of two fine, interrupted catgut sutures passed through

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the sheath. He advised leaving the catgut entirely within the duct. Dickinson,⁷ in 1927, used a strand of silkworm gut which was allowed to project into the mouth. He fixed the strand at its point of entrance into the mouth by a suture. Black and Flagge,⁴ in 1928, used a small ureteral catheter to act as a dowel, leaving about 1 inch of the catheter extending into the mouth. Butler and Guinan,⁵ in 1933, also used a ureteral catheter as a dowel, anchoring it to the canine tooth of the upper jaw with a silk ligature. Brohm and Bird,⁶ in 1935, brought the dowel out through the cheek and sutured it to the skin. Newman and Seabrook,⁸ in 1946, reported the use of tantalum wire as a dowel, bringing it out of the mouth and taping it to the cheek. Fixing the dowel in the duct has been the most difficult problem. In the technic used by the authors this difficulty has been removed.

GENERAL CONSIDERATIONS IN TREATMENT

Injuries of the parotid duct and gland may occur in one of three areas (1) over the parotid gland, (2) over the masseter muscle, and (3) in the buccinator muscle area.

Fistula of the glandular area. Many fistulas of the smaller ducts of the gland will heal spontaneously. Roentgen therapy and cauterization of the wound sometimes will produce healing. Fistula in the larger ducts of the gland may be treated in the manner to be described.

Fistula over the masseter muscle. The majority of parotid duct fistulas occur in this area and can be treated easily and quickly by the technic described in this paper.

Fistula in the buccinator area. Injuries in this area often have been treated by short-circuiting operations that cause the saliva to flow into the mouth proximal to the papilla. This method does away with the valve-like action of the papilla and there is no protection against ascending infection from the mouth. The authors believe that every attempt should be made to preserve the papilla. The technic used by us was found to be satisfactory in repairing lacerations in the buccinator area.

TECHNIC

Preoperative. Good oral hygiene should be maintained and a mouth wash used every two hours, beginning immediately after the diagnosis is made and continuing until the time of operation. Penicillin may be used intramuscularly for 24 hours before surgery.

Operative. After the skin has been cleansed and a mouth wash used, the face is draped. Local anesthesia then is injected into the skin surrounding the laceration or fistula. An incision about $1\frac{1}{2}$ cm in length is made through the skin, care being taken to avoid the nerves and vessels that lie next to the duct. A probe is then passed through the mouth, into the papilla and along the duct toward the incision. The end of the probe is brought out through the incised wound and a strand of cotton thread size No. 10 (or heavy silk) is fastened to it. The threaded probe is then pulled back through the duct into

FISTULAS OF PAROTID DUCT

the mouth. The patient is given a few drops of lemon juice to stimulate the salivary flow. It is then usually easy to identify the proximal end of the severed duct in the incision. The end of the cotton or silk strand is threaded

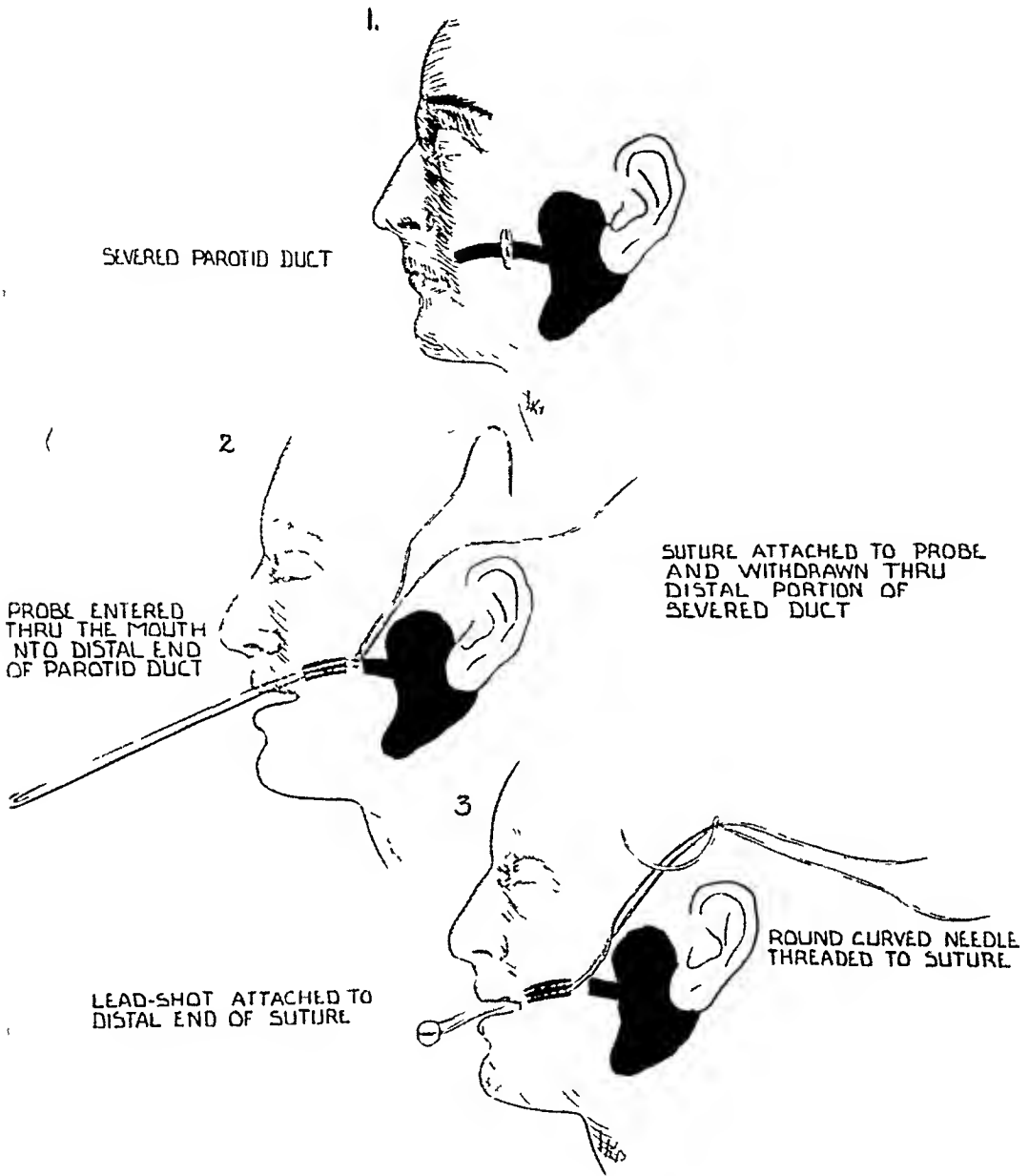


FIG 1—First 3 stages of repair of parotid duct

on a long Mayo needle and the needle passed backwards, blunt end first, into the proximal duct. With gentle manipulation the needle is forced through the parotid gland to the skin. A tiny nick is made in the skin and the thread carried through (Fig 1).

A lead shot applied to each end of the thread holds it snugly in place. A small square of rubber sheeting inserted between the mucosa and the lead pellet will prevent irritation.

The tissues in the incision are approximated with interrupted catgut sutures and the skin closed without drainage (Fig 2)

Postoperative Care The patient should continue to use a mouth wash frequently His oral hygiene must be supervised carefully and fluids given

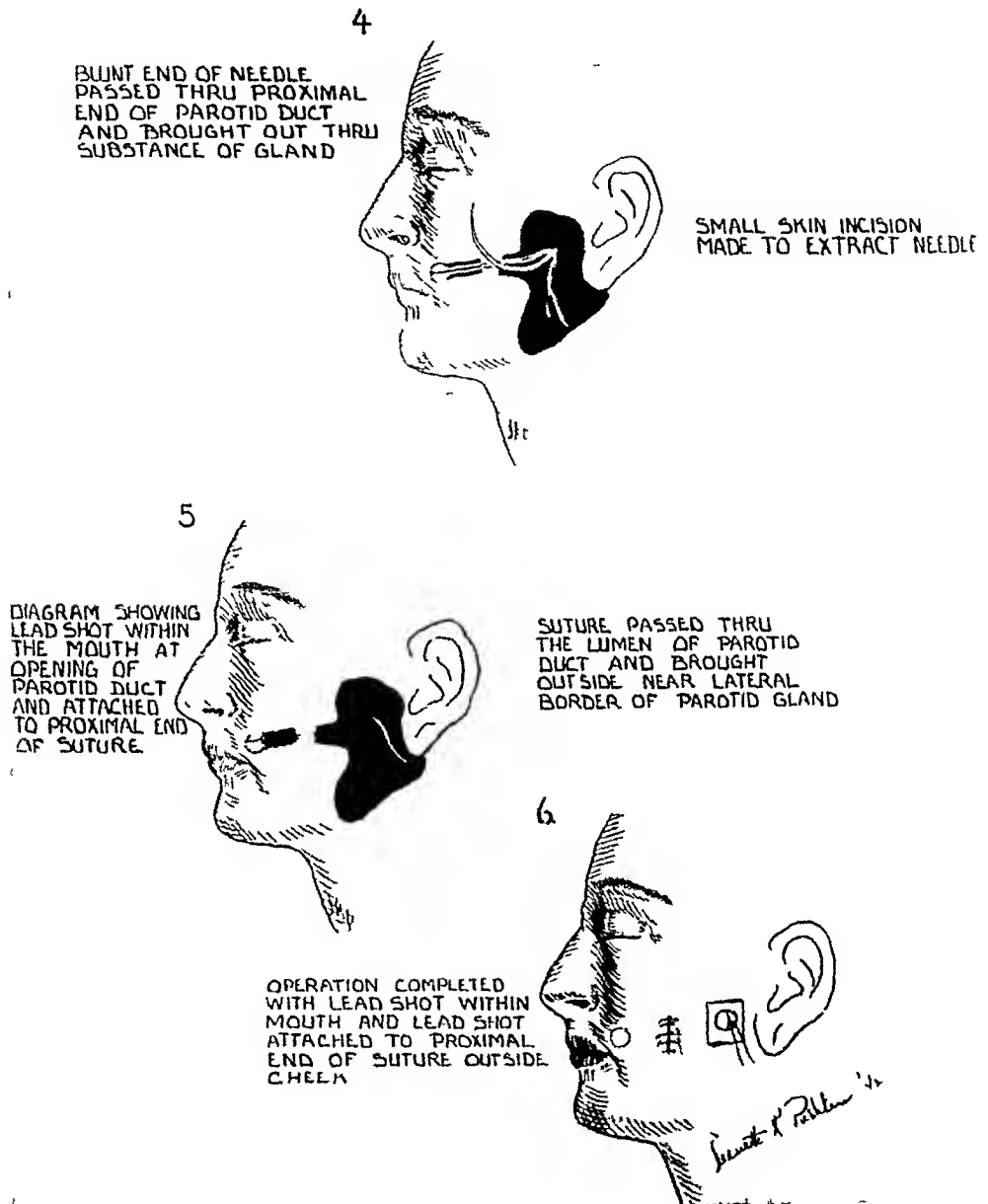


FIG 2—Last 3 stages of repair of parotid duct

freely Penicillin may be given intramuscularly for several days following operation As a rule, a watery fluid will drain from the incision for about a week Swelling that is not of inflammatory origin may be disregarded

The sutures usually are removed from the wound at the end of seven days The cotton or silk dowel should not be removed until the 14th postoperative

day Salivary juices usually enter the mouth through the duct soon after operation, and it will be noted by the patient that the buccal mucosa on the injured side no longer is dry

CASE REPORTS*

Case 1—D H, white, male, age 28, received treatment July 11, 1942, for numerous lacerations of the left side of the face and neck, also the left shoulder. When seen later (July 15), there was moderate swelling of the left side of the face. The patient stated that his dressings became soaked with a water-like substance when he ate. A diagnosis of laceration of the parotid duct was made. Warm compresses were applied to the inflamed area for several days but the drainage persisted. Operation for the repair of the lacerated duct was performed July 21, 1942, using the technic described. Postoperative treatment consisted of sulfathiazole, a perborate mouth wash at regular intervals, and a liquid diet. The swelling of the left cheek persisted for three days. At the end of this period saliva began entering the mouth freely. The suture was removed August 14. The patient was discharged six days later, the gland and duct functioning normally.

Case 2—A M, colored, male, age 35, received a knife laceration of the left side of the face just in front of the ear. The wound was sutured by his local physician. One week later, according to the patient, a large tender mass was noted just anterior to the left ear. The patient stated that the mass increased in size on mastication.

Operation was performed Oct. 31, 1941, in accordance with the technic described. Saliva was seen coming through the duct into the mouth a few hours after operation. The patient was discharged Nov. 4, with a normally functioning duct. The suture was removed three weeks later. The wound had completely healed and no swelling was present.

Case 3—R T, colored, male, age 48, was admitted to the hospital after receiving multiple lacerations of the left side of the face and neck. The most severe of the lacerations extended across the left cheek from the base of the ear to the upper lip. The lacerations were sutured shortly after admission. Several days later prominent swelling of the left side of the face was noted. Fluid aspirated from the swollen area was found on examination to contain amylase.

Sixteen days after admission the divided Stensen's duct was repaired, employing the usual technic. The duct was found to be completely severed as was a small portion of the parotid gland itself. There was generalized oozing of saliva from the entire lacerated portion of the gland. Following operation the face remained swollen for a few days, a scant flow of saliva escaping through the incision. Approximately one week after operation the swelling had completely subsided, saliva flowing freely into the mouth. The suture was removed on the 12th postoperative day.

Case 4—E O, white, male, age 39, was admitted to the hospital complaining of a watery drainage from his left cheek at the site of a sutured laceration in this area received 20 days earlier. The patient stated that the drainage was most noticeable during meals.

Surgical repair of the lacerated duct was carried out Nov. 19, 1947, in accordance with the method described. Drainage from the incision ceased about the 4th postoperative day, saliva flowing freely into the mouth. The suture was removed on the 15th postoperative day, the parotid duct and gland having continued to function normally.

Case 5—A N, white, male, age 69, was admitted to the hospital August 1, 1945, with a tumor just anterior to the left parotid gland. The patient stated that the tumor had been present since about the time of the first world war. A mixed tumor 7 by 3 by 2 cm was removed August 2, 1945. A few days later drainage from the operative incision was noted. A diagnosis of parotid duct fistula was made.

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Surgical repair of the fistula was carried out August 19, 1945, and the technic used was that suggested by the authors. The drainage from the previous operative incision ceased within a few days following repair of the fistula. When the patient was last seen both wounds were dry and well healed.

SUMMARY AND CONCLUSIONS

Salivary fistulas of the parotid duct and gland respond to treatment if certain principles are observed, the most important of these being the use of a dowel to splint the severed duct. A simplified method of anchoring the dowel is described. The duct papilla must be preserved if possible. Five cases in which successful results were obtained using the authors' technic are reported.

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ACUTE DIVERTICULITIS OF THE CECUM*

REPORT OF THREE CASES DIAGNOSED PRE-OPERATIVELY
AS ACUTE APPENDICITIS

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OUT-POUCHINGS OF THE COLON of various sizes, shapes, positions, and types occur very frequently throughout the population at large. The exact number can be only estimated because of the obviously large number which are never diagnosed. This is largely due to the fact that they cause no symptoms to necessitate the individual either being subjected to roentgenologic examination with a barium enema, or to gastro-intestinal studies as a result of abdominal complaints. Those found at autopsy represent a very small percentage of the total population. A few are found as incidental findings at operation. In routine autopsies, Mayo²⁵ reports from 5 to 7 per cent of all the colons examined revealed diverticula some place throughout their entirety. Epstein⁸ quotes Sprigg and Marker to show that out of 1,000 routine roentgen-ray examinations of the colon, 100 diverticula were found. The location of each showed about 58 in the pelvic colon, 46 in the descending colon, 16 in the transverse colon, 10 in the ascending colon, 7 in the cecum, 5 in the appendix, and 3 in the rectum. Anderson¹ reports a 5.7 per cent occurrence of the diverticulosis of the colon noted in routine roentgenologic examinations, and 6.9 per cent occurrence of diverticulosis in routine autopsies.

Diverticulosis is the term used to denote those silent out-pouchings of the colon with small necks and lined by mucosa, in which there is no evidence of inflammation or symptoms referable thereto. When these blind sacs become inflamed, either because of obstruction or other causes, the diagnosis of diverticulitis must be made. Bennett and Jones⁴ estimate that in only 12 to 15 per cent of the cases of diverticulosis, does inflammation occur to justify the diagnosis of diverticulitis. Ochsner and Barger¹⁹ found that in 2 per cent of 151 cases of uncomplicated diverticulosis of the colon, the diverticula were present in the right half of the colon, and that about 14 per cent of all diverticula become inflamed, and 15 per cent of these inflamed diverticula were subjected to surgery. From this it is seen that acute diverticulitis of the cecum meriting surgical intervention is not a rare condition. Various authors have reported and reviewed cases appearing in the literature since the first case was reported by Patier in 1912. In 1944, Noon and Schenk²⁷ reported 48 cases and added three of their own. These cases were taken from the American and British literature and represented the highest number of cases noted to that date until Anderson's¹ recent, most comprehensive review, in which 91 cases of acute diverticulitis of the cecum were reported from the literature. To

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these he added nine cases. These nine cases of acute diverticulitis of the cecum were among some 700 cases of surgical diverticula of the colon at the Mayo Clinic.

The three cases of acute diverticulitis of the cecum herein presented were seen on the surgical service of this Veterans Administration Hospital within a 12 months' period, all three were diagnosed preoperatively as acute appendicitis, all were subjected to surgery. An acutely inflamed true diverticulum was found in each, and in two cases rupture of the diverticulum with abscess formation was encountered. These cases will bring the total of those reported to over 100, and will help to disprove the previously held belief that this is a rare surgical entity, and should impress the surgeon that it is one which must be kept constantly in mind when the diagnosis of right-sided abdominal pathology is made preoperatively. It also must be considered when the pathologic condition of the appendix found at operation is not sufficient to explain the signs and symptoms leading to preoperative diagnosis of appendicitis.

In a patient presenting signs and symptoms characteristic of appendicitis, in whom an appendectomy has previously been performed, the diagnosis of acute diverticulitis of the cecum must be considered as a very real possibility.

The average age incidence of this disease is given by different authors to be approximately 40 years. In our cases, all the patients were males due to the character of the hospital in which the cases were seen. Their ages were 25, 35 and 30, respectively. It has been noted in the past that there has been a preponderance of males reported with this condition. However, Anderson¹ finds about an equal number of each sex with this disease.

The cause of diverticulosis and subsequent diverticulitis is not definitely established, but Greensfelder and Hiller¹⁵ suggest that any one, or several, of the following mechanisms may be important as a causative agent: (1) eversion of the cecal wall between two constricting bands, (2) traction by abdominal adhesion (usually postoperatively), (3) eversion of a weak spot in the cecal wall, caused by migration of a purse string suture into the lumen of the intestine (postoperatively), (4) eversion of the weakened area in the cecal wall, resulting from the rupture into the cecum of an abscess of the appendiceal stump, (5) weakening of the wall of the bowel at the site of entrance of blood vessels into the muscularis, (6) increased intraluminal pressure in the cecum, either due to constipation or increased intraabdominal pressure, (7) inherent weakness of the wall of the bowel due to age, congenital weakness, obesity or atrophy of the fat along the vessels which penetrate the wall, (8) traction on appendiceal epiploicae, mesentery or omentum, with or without adhesions, (9) traumatic diverticula following previous operative procedure, especially appendectomy (this type is classified as "Secondary Diverticula"), (10) retention in residual form of the appendix which appears in embryologic life but normally disappears before the true appendix develops, (11) cathartics, etc.

The preoperative diagnosis is, in the great majority of the cases, acute appendicitis and operation is carried out for alleviation of that condition. The following preoperative diagnoses have been made: Acute appendicitis, gan-

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grenous appendicitis, perforating appendicitis, appendiceal abscess, subacute appendicitis, chronic appendicitis, uterine fibroid (degenerated), salpingitis, carcinoma of the cecum, diverticulitis of the right colon, obturator hernia, stump appendicitis, abscess of undetermined origin and benign ulcer of the cecum

In approximately one-third of the reported cases, histories of previous attacks of right lower quadrant pain were elicited. The most usual complaint of patients is pain in the right lower quadrant, either localized or generalized. Pain may be of a cramping or dull aching type and it was present in various patients for periods of a few hours to several days. The general observation has been made by several observers that in acute diverticulitis of the cecum, the pain is less severe and more prolonged, and shows a more chronic course in contradistinction to acute appendicitis where the pain is more acute, and of shorter duration. However, this is purely an impressionistic finding. Other symptoms noted with more or less frequency are: Tenderness in the right lower quadrant, mass in right side of the abdomen, rebound tenderness, psoas tenderness and tenderness over the entire abdomen.

The differential diagnosis, preoperatively, is not easy because of the many diseases which this condition resembles. When a diagnosis of an acute surgical condition in the abdomen is made, roentgen-rays are of little value and are contraindicated. The laboratory work has proven to be of very little help in differential diagnosis, as the same picture is noted here as is noted in acute appendicitis. A leukocytosis may or may not be present. Usually there are no urinary findings which are of any help. Also, if roentgen-ray examination of the colon were made, it would be ineffective in demonstrating diverticula which are plugged by feces, fecaliths, or pus, causing visualization to be impossible. Thus, it is seen that a differential diagnosis of acute diverticulitis of the cecum as against acute appendicitis cannot be made, but it is a condition which should constantly be kept in mind by the diagnostician and operating surgeon.

Diverticula may be divided into two groups. True diverticula are those in which all normal layers of the intestine, including the mucosa, submucosa, muscularis, and serosa are present over the entire diverticula, the false or acquired type are those in which the muscularis is absent, the other layers being present. It is believed that false diverticula represent out-pouchings through weak points in the muscularis of the bowel. The true diverticula are probably congenital. All three of the cases here reported were true diverticula, as shown by the presence of all layers on microscopic pathological examinations. Diverticula in the cecum, when present, are usually not associated with the presence of diverticula throughout the remaining portion of the large bowel. The majority of those cases reported are the true type and are solitary. Two of the cases here reported are true solitary diverticula, the third is a true type but multiple.

CASE REPORTS

Case 1 A 25-year-old white male entered the hospital on June 13, 1946, with a history of abdominal cramps of 48 hours' duration, most marked in the right lower

quadrant and slight nausea over the same period of time. There was no vomiting, diarrhea or increase in temperature noted by the patient. On examination, generalized abdominal tenderness was noted, which was localized and most marked in the right lower quadrant. Slight rigidity and slight rebound tenderness were noted in the right side of the lower abdomen. Rectal examination revealed no mass, but some tenderness in the right lower quadrant was present. The leukocyte count showed 13,200 cell per cubic mm of blood with 62 polymorphonuclear leukocytes. The examination of the urine revealed no abnormal findings. His admission temperature was 99.5°F. A preoperative diagnosis of

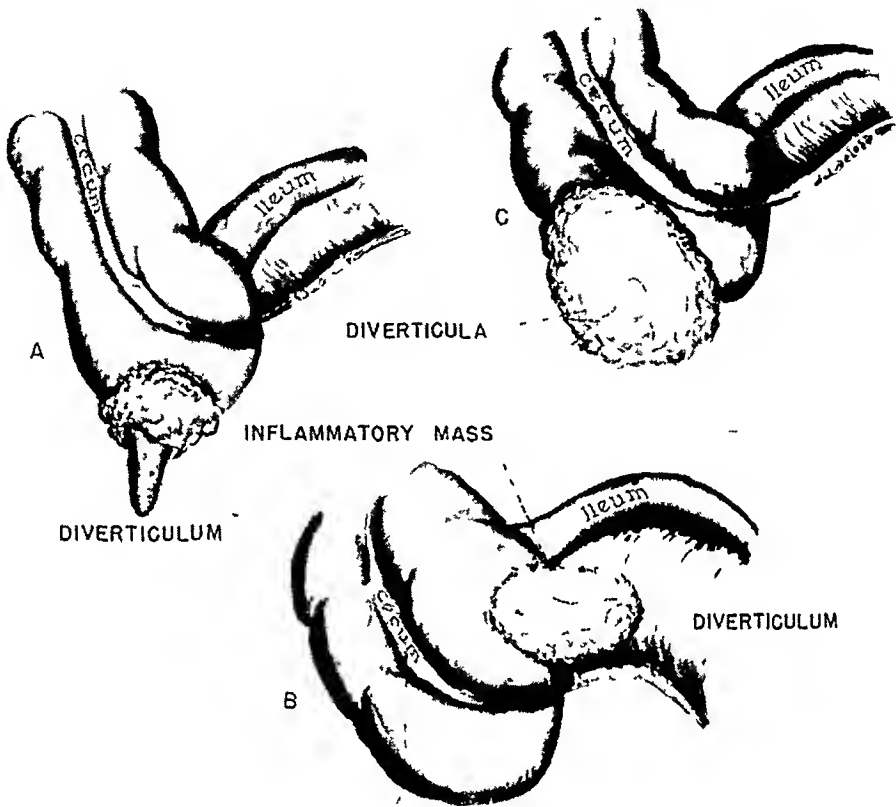


FIG 1—A illustrates the location and appearance of the lesion in Case 1—an inflammatory mass at the base of the diverticulum without perforation. B shows the perforated diverticulum within an inflammatory mass—involving the meso-appendix encountered in Case 2. C double diverticula within a walled-off abscess as seen in Case 3. One of the diverticula is perforated at its tip.

acute appendicitis was made. At operation, which was performed by Dr. D. J. Abramson, the appendix was found to be in a normal position and not inflamed. There was a mass, measuring 3 by 4 centimeters in the redundant portion of the cecum. This mass was located opposite the ileo-cecal valve on the anterior lateral aspect of the cecum, near the free tenia of the colon (Fig. 1A). On careful investigation, this mass was found to have in its center a markedly inflamed diverticulum of the cecum containing a fecalith and a considerable amount of fibrinous exudate at its base. The diverticulum, which was not perforated, was amputated at its base and the defect in the colon closed with purse string type inverting cat gut suture in the serosa and this was reinforced by interrupted sutures. The appendix, which was not abnormal, was also removed. The abdomen was closed without drainage and without chemotherapeutic agents in the peritoneal cavity. The convalescence was uneventful and the patient was discharged from the hospital 8 days later. The

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pathological examination showed a marked inflammatory process throughout the wall of a true diverticulum which contained mucosa, muscularis and serosa. The appendix showed no pathologic changes. Follow-up barium enema studies of the colon revealed no further diverticula.

Case 2 A 35-year-old white male admitted to the hospital February 13, 1947, with the complaint of abdominal pain, aching in character, which has been present in a mild degree intermittently for several years. The day before admission, the pain became much worse and was confined predominantly to the right lower quadrant. He noted no radiation of the pain. There was no vomiting or nausea. He had a history of normal bowel



FIG 2—X-ray examination of colon with barium enema showing one additional small diverticulum on the medial aspect of the ascending colon near the hepatic flexure

movement on the day previous to admission. He felt some burning on urination but no other prominent genito-urinary symptoms. His temperature on admission was 98.6°F. Examination revealed marked tenderness in the right lower quadrant, slight rigidity, moderate rebound tenderness with a positive psoas tenderness noted in the right lower quadrant. Laboratory findings on admission revealed a white blood cell count of 11,250 per cubic mm of blood, with 69 polymorphonuclear cells. The urine examination was negative. A preoperative diagnosis of acute appendicitis was made. The operation, which was performed under spinal anesthesia, was carried out through a McBurney type incision. There was no free fluid present. Upon mobilization of the cecum, the appendix was noted to be greatly elongated but not markedly inflamed. At a point about one-half inch distal to the appendix on the medial aspect of the cecum, there was large firm inflammatory mass the size of a hen's egg involving the meso-appendix (Fig 1B). This mass

was carefully dissected from the cecum along its serosal covering and a gangrenous diverticulum was noted. This gangrenous mass was tightly adherent to the cecum and was made up of inflammatory tissue covered tightly by meso-appendix and in its center was the perforated tip of the diverticulum. The entire mass was excised at the base of the diverticulum. The defect in the cecum was closed with interrupted catgut sutures and reinforced with #60 cotton sutures. There was no spillage into the peritoneal cavity and no evidence of generalized peritonitis. The appendix was removed routinely. The abdomen was closed without drainage and without the institution of chemotherapy. The patient's convalescence was not remarkable and he was discharged from the hospital 15 days postoperatively. Roentgen-ray study of the gastro-intestinal tract and a barium enema examination of the colon postoperatively revealed no evidence of diverticula throughout the rest of the colon. Pathologic examination revealed a small sac-like structure which contained many blood vessels, eosinophils, polymorphonuclear and lymphocytic infiltration throughout the walls, layers of muscularis, mucosa and serosa were noted and a diagnosis of gangrenous diverticulum was made.

Approximately two weeks following the patient's discharge from the hospital, he was readmitted with complaints of fever, chills and swelling in the right lower quadrant. Physical examination at this time revealed a tender, firm mass beneath the recent McBurney scar. Temperature was 101.4°F on admission. Examination was otherwise negative. After conservative treatment with wet packs and chemotherapy for a few days, the mass was opened surgically under sodium pentothal anesthesia and was found to be a subcutaneous hematoma. This was drained and no evidence of inflammation, exudate or pus was noted. Patient was discharged 20 days later, completely well.

Case 3 The patient was a 30-year-old white male who entered the hospital on May 20, 1947, with a history of awakening in the morning with soreness in the right lower quadrant which continued without relief up until the time of examination. There had been no nausea or vomiting. His bowels had moved normally the day before. He had had no history of similar attacks, no hematemesis, jaundice or other GI complaints. He had a history of recurrent attacks of malaria since his discharge from the service. His temperature on admission was 99.6°F. Examination revealed moderate tenderness on deep palpation in the right lower quadrant with rebound tenderness referred to McBurney's point. There was no spasm and no palpable mass. Urine examination, on admission, showed an occasional coarse, granular cast, otherwise it was negative. Subsequent urine examination showed an occasional hyaline cast, another coarse granular casts, from 5 to 6 white blood cells, and 10 to 12 red blood cells per high power field. His serology was negative. Examination of his blood showed a white blood count of 12,400 cells per cubic mm of blood with 75 polymorphonuclear cells. A diagnosis of acute appendicitis was made. The operation was carried out under spinal anesthesia through a transverse incision in the right lower quadrant. There was no free fluid present in the peritoneal cavity. A firm mass, the size of a hen's egg, was found bound down in the right gutter on the lateral aspect of the cecum (Fig 1C). Inspection revealed the appendix to be lying free and not involved in the mass and not inflamed. The cecum was mobilized with difficulty, and the cecum and mass exteriorized. The mass was dissected from the cecum and in its center was found a ruptured diverticulum with abscess formation. The appendix was somewhat inflamed. The diverticulum was on the posterior lateral aspect of the cecum, approximately 1½ inches lateral to the base of the appendix. It had a broad base and its tip was divided to form two separated diverticula, one of which was inflamed and the other of which was perforated and involved in the before-mentioned mass. The wide base of the two diverticula was clamped, the mass excised, and the defect in the cecum closed with an inverting type of catgut suture reinforced by #40 interrupted cotton sutures. The appendix was removed in the routine manner. Inspection of the remaining exposed portion of the colon revealed no further diverticula. The abdomen was closed without drainage and no chemotherapy instituted. The pathologic examination

showed the specimen to be a true diverticulum containing all layers of small intestine with necrosis of the epithelium and diffuse invasion of the wall by leukocytes in the muscularis. Convalescence was uneventful and the patient was discharged approximately 17 days postoperatively. At this time a gastro-intestinal roentgenographic study was made, as well as a barium enema examination which revealed a small diverticulum on the medial aspect of the ascending colon, just below the hepatic flexure (Fig 2). There was no other evidence of diverticula or pathology.

COMMENT

It is seen from these cases that acute diverticulitis of the cecum closely resembles an acute appendicitis in all respects and behaves very similarly in the abdomen. Abscess is usually formed at the site of perforation and very rarely causes generalized peritonitis. The omentum frequently acts to localize the exudated material and holds it in check to form abscesses similar to those noted in two of these cases. The abscesses often lie adjacent to the mesentery or between its leaves. These thick-walled abscesses are closely associated with the cecum and often become tumefied and associated with large mesenteric lymph nodes to the extent that differential diagnosis of malignant tumors of the cecum is very difficult, if not impossible, even at operation. This is a very important fact because, as is well known, carcinoma of the cecum is much more common than diverticulitis of the cecum. Consequently, unless the accurate diagnosis is made by the operating surgeon, the improper operative procedure may be carried out and a radical resection of the cecum and ascending colon done in the belief that the lesion at hand is a carcinoma, whereas in reality it may be an inflamed diverticulum and a simple resection of the local lesion is all that is necessary. On the other hand, since diagnosis of carcinoma of the cecum is a much more formidable one and the sequelae carry such a high mortality, error in the opposite direction should also be guarded against. Most patients subjected to surgery for diverticulitis of the cecum recover. The mortality rate is given as 6 per cent.

At operation the usual finding is a single diverticulum with a narrow neck in the outer portion of the cecum. It may have become congested by concretions of fecalith and obstructed and the neck traps pus in the blind sac. Since the muscularis is often absent or very deficient there is no pressure to force the fecalith or blocking concretion out of the neck and thus obstruction and strangulation result. This set of circumstances differs from the normal functioning appendix which is able, in numerous cases, to empty itself. Due to this bottle neck formation and stasis and an increased absorption of water in the right colon, fecaliths are more liable to form and give rise to acute inflammatory reaction here. Jonas¹⁶ found fecalith present in 68.4 per cent of his cases. A fecalith was present in only one of the cases reported in our series of three.

Local sequelae following acute diverticulitis of the cecum may be (1) Perforation with localized or generalized peritonitis, (2) gangrene of the diverticulum, (3) abscess formation, usually involving the right portion of the cecum, peritoneum in the right lower quadrant, and omentum, (4) multiple adhesions in the area of the diverticula, (5) entero-intestinal fistula, or

entero-vesicle fistula, or entero-colic fistula, or others, (6) retrocecal abscess, (7) extra-peritoneal abscess

There may be a diverticulitis with intestinal obstruction or there may be diverticulitis associated with a carcinoma of the cecum, so both should be kept in mind at the time of operation. Upon palpation of a mass in the cecum at the time of operation, an examining finger may be placed in the opposite wall of the cecum and the surgeon may feel a defect or hole in the mass at the site of the base of the diverticulum, and this may give some aid in differentiating it from a carcinoma.

The other diseases which must be considered and differentiated from acute cecal diverticulitis are Acute appendicitis, carcinoma of the cecum, actinomycosis of the cecum and right side of the bowel, and intussusception.

The microscopic pathology usually noted is gangrene of the mucosa with ulceration, inflammation of the muscularis with thickening and edema, with infiltration of blood vessels, and increase in the leukocytes in the subserosa, as well as fragmentation of the muscularis, and a generalized inflammatory picture. Perforation is much more likely if the muscularis of the bowel is absent in the diverticulum proper.

The treatment should be such that the minimal operative procedure is carried out to effectively eradicate the pathology present. The plan of treatment necessarily depends on the type and extent of the lesion, as follows: (1) Simple excision of the involved diverticulum with closure of the defect in the cecum (similar to the procedure carried out in routine appendectomy) can be done if too much of the bowel wall is not involved. In this respect, our experience is compatible with that of Gatewood¹² in that the tissue edges of the bowel were normal despite the gangrenous character of the diverticulum itself, and closure of the cecal defect could be carried out with ease by a purse string-type suture. However, if edema and thickening of the cecal wall in the area of the diverticulum is marked due to abscess formation and gangrene, as reported by Frehling,⁹ closure of the cecal defect is difficult and more extensive resection of the cecum may be necessary to get an effectual closure. (2) Simple closure of the defect after a perforation has occurred by invagination of the stump and suturing normal serosa to serosa at the base of the cecum is simple and often adequate. (3) Right colectomy will be necessary if too much of the cecum and ascending colon is involved in inflammatory and gangrenous mass and it is evident that any lesser procedure would jeopardize the patient's welfare, or would add to the spread of infection or increase morbidity or mortality. This should be used as the last resort. However, Jonas¹⁶ points out that very large inflamed diverticula lying close to the ileo-cecal valve or between the leaves of the mesentery, so as to jeopardize the cecal blood supply, require extensive resection, including the terminal ileum and ascending colon, with an anastomosis between the ileum and transverse colon. (4) Drainage of an abscess is the only practical procedure when present, or an inflammatory mass adherent to the terminal ileum, rest of cecum, and peritoneum to such an extent that attempt at resection would spread the infection and increase the

morbidity (5) Exteriorization of the mass in a Mikulicz's type of procedure has been recommended when the cecal wall is gangrenous to such an extent that to return the cecum to the abdominal cavity would be unthinkable. At a later date, the ileo-colostomy would then have to be closed. An alternate procedure, recommended by Frehling,⁹ is to simply exteriorize the portion of the cecal wall which is gangrenous, form a cecostomy and allow the gangrenous portion of the cecum to slough, this results in a subsequent fistula, which may close itself or require minimal operative procedure at a later date. (6) Resection of the cecum may be necessary in cases where the cecum alone is involved and the terminal ileum and ascending colon appear to be in fairly good condition. If the blood supply to neither is jeopardized, the cecum itself may be resected and a side-to-end anastomosis be done between the terminal ileum and ascending colon just above the cecal region. (7) Schung²² advises conservative treatment with chemotherapy without resection if the clinical diagnosis can be made, on the rationale that the majority of the lesions would drain into the bowel and subside spontaneously. This is not recommended for a routine procedure.

CONCLUSION

Acute diverticulitis of the cecum is not as rare a disease as was previously believed, as evidenced by a total of now more than 100 cases in the literature. It must always be considered in patients exhibiting right lower quadrant pain and in whom a preoperative diagnosis of appendicitis is made. There is close resemblance to appendicitis in its pathology and action in the abdomen, which makes surgery the treatment of choice in this disease in all cases. Usually at operation for appendicitis, when a non-involved appendix is found, the possibility of cecal diverticulum, as well as a Meckel's diverticulum, must be considered. The operative procedures which have been recommended are given. The differential diagnosis, preoperatively, between acute appendicitis and diverticulitis of the cecum cannot be made. At operation, the differential diagnosis between the much more frequent carcinoma of the cecum, and diverticulitis of the cecum is very difficult to make. A careful evaluation must be made by the surgeon to avoid either a too radical resection for a minimal disease or a too limited resection in the case of a carcinoma, which merits the widest type of excision. Differentiation of this condition from a fibrosing type of tuberculosis of the cecum, from actinomycosis of the cecum and appendiceal abscess requires knowledge, experience and skill. Great care should be exercised in an attempt to carry out the correct procedure in each case. The condition may be present at any age in either sex, in fairly equal numbers, and if properly treated the mortality rate is low. The complications and sequelae are listed above. The one case reported here in which a hematoma of the abdominal wall resulted postoperatively is not a true sequela of the disease since there was no evidence of infection and it was obviously an error in hemostasis at time of operation.

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THE USE OF FULL THICKNESS SKIN GRAFTS IN THE REPAIR OF LARGE HERNIAE*

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THE PROBLEM OF REPAIR of the abdominal wall in patients with large hernial defects has taxed the ingenuity of the surgeon for many years. The procedures described attest by their number and diversity to the fact that no single satisfactory method has yet been found. It is the author's opinion that the use of full thickness skin as a buried graft in the repair of large herniae may be the answer to what has been, in some cases, an almost insoluble problem.

Skin, minus the epidermal layer, is known as cutis. Loewe¹ and Rehn² first advised using cutis in the repair of postoperative abdominal herniae. Cutis has been used extensively and almost exclusively in the United States by Cannaday.³ Cutis is elastic and contains a rich network of connective tissue fibres. When it is stretched and sutured under tension as a buried graft it soon undergoes metaplasia into firm connective tissue. Biopsies taken four years after cutis had been buried in deep tissues showed histological evidence of normal connective tissue, with no sign of retention cysts, hair follicles or sebaceous glands (Uihlein⁴). These findings have been confirmed by Peer and Paddock⁵ who, after scraping the epidermis, buried free skin grafts in the chest walls of human subjects. The grafts were removed for study at periods ranging from seven days to 12 months. They found marked connective tissue response at the site of implantation. Sweat glands were replaced by fibrous tissue and sebaceous glands had disappeared. Mair⁶ operated upon a man three months after he had used a full thickness skin graft in the repair of an inguinal hernia and noted that it was difficult to tell where the graft began since metaplasia into connective tissue was so profound. Histologic examination of the tissue showed highly vascular connective tissue with no identifiable dermal or epidermal elements. The graft was richly infiltrated with collagen and elastic fibres and was firmly adherent to the underlying muscle. No macroscopic or microscopic cysts or hair follicle remnants were seen. A few giant cells were present.

The findings of Mair and of Peer and Paddock indicate that full thickness skin is as efficacious as cutis and that the danger of inclusion cysts forming in the buried graft is negligible. Do wounds in which skin has been buried show an increased liability to infection? Harkins,⁷ in listing his objections to the use of cutis, named infection from organisms in the hair follicles and sudoriferous glands. However, Mann⁸ in 1945 reported only two cases of mild sepsis in 137 hernial repairs in which he had used whole skin grafts. In 1946 the same author⁹ stated that the incidence of wound sepsis and hematoma was no greater with this method than in any of the standard types of repair.

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Is whole skin preferable to cutis if one adopts the use of skin as a method of hernia repair? Whole skin is easier to obtain than cutis, operating time is consequently shortened. If removal of the epidermal layers of the skin is not necessary to prevent infection or the formation of inclusion and retention cysts there is apparently no reason for not using whole skin instead of cutis.

Harkins⁷ has said that in his opinion the bridging of defects in incisional or ventral herniae is seldom necessary and that he "has never seen a ventral or incisional hernia where the fascial layers could not be brought together." However, two of the author's small series of cases were incisional herniae secondary to shell fragment wounds of the abdomen, in which there had been such extensive loss of tissue in the abdominal wall that it was impossible to approximate peritoneum or fascia. It is true, of course, that such large defects are seldom seen in civilian surgery, but we believe that some of the recurrences seen after the repair of ventral and incisional herniae are probably due to the cutting through of sutures tied under tension in an effort to approximate fascial gaps. We prefer in such cases to use whole skin to bridge the fascial gap. We also believe that skin should be used to reinforce the repair in large herniae even when fascia can be mobilized.

CASE REPORTS

Case 1—J H Age 28, male. Large hernia in left upper abdominal quadrant following laparotomy for shell fragment wound of abdomen. At operation in January, 1946, a defect in the peritoneum and fascia measuring 3 by 5 inches was found. The fascia could not be approximated. A full thickness skin graft was used to cover the defect. Postoperative course was uneventful. The patient was seen in July, 1948, at which time the repair was intact and the patient asymptomatic.

Case 2—F E Age 24, male. Left upper abdominal hernia following laparotomy for shell fragment wound of abdomen. At operation in March, 1945, a defect in the fascia was found, measuring 4 by 3 inches. The fascia could not be approximated. Full thickness skin graft repair was done. Uneventful postoperative course. A letter received from the patient in Aug., 1948, stated that he was well and had no evidence of recurrence.

Case 3—H F Age 45, male. Incisional hernia in right upper abdominal quadrant. At operation in May, 1946, a fascial defect was found measuring 3 by 5 inches. Partial fascial approximation was done with a full thickness skin graft to complete the repair and reinforce the fascia. Patient was seen in August, 1948, with no evidence of recurrence.

Case 4—H K Age 51, male. An extremely obese man with a large incisional hernia in the right upper abdominal quadrant, of 18 years duration. At operation in September, 1946, a fascial defect measuring 4 by 4 inches was found. The fascia around the margins of the ring was extremely thin and frayed out. The fascia was approximated and a full thickness graft used to cover the area. This patient developed a large collection of serum in the wound which became grossly infected, necessitating incision and drainage. The repair remained firm and when seen in August, 1948, there was no evidence of recurrence.

Case 5—M P Age 26, male. This patient had a large, recurrent direct inguinal hernia. At operation in September, 1946, there was a very large direct hernia with complete deficiency of the transversalis fascia. Repair was effected by suture of a flap of rectus sheath to Cooper's ligament, supplemented by a free full thickness skin graft behind the cord. Patient was seen in July, 1948 with no evidence of recurrence.

Case 6—W L Age 53, male Entered hospital for treatment of a bleeding duodenal ulcer and repair of a large incisional hernia in the right upper abdominal quadrant In September, 1946, an infra-diaphragmatic vagotomy was done and the hernia repaired by approximation of the fascia and a full thickness skin graft Postoperatively the patient developed massive pulmonary atelectasis and marked pylorospasm with prolonged gastric retention In spite of intensive therapy including administration of urethane betamethylcholine hydrochloride and posterior gastroenterostomy the patient went steadily downhill and died in December, 1946 The hernia repair remained firm throughout and was intact at postmortem examination

Case 7—J P Age 71, male Patient had a huge direct inguinal hernia He was transferred to the surgical service after a perineal prostatectomy and operated upon in September, 1947 At operation a very large direct hernia was found, with complete deficiency of the transversalis fascia A flap of rectus sheath was sutured to Cooper's ligament and a full thickness skin graft placed behind the cord The patient was discharged in 9 days with a firm repair The patient was seen in Aug, 1948, and had no evidence of recurrence

SUMMARY

A review of the use of full thickness skin grafts in the repair of large hernial defects has been presented A small series of cases has been cited, largely in an attempt to stimulate interest in a method which has not been used extensively in this country and which the author believes has great merit By using skin, both as the sole tissue in repair, or as a supplement to inadequate fascial closure, difficult plastic procedures may often be avoided This is especially desirable when the contemplated method of repair involves shifting or free grafting of large flaps of fascia with subsequent secondary fascial defects The procedures used are simpler and less time consuming than the usual plastic fascial repairs Whole skin grafts proved efficacious in several cases in this series which would have been extremely difficult to repair by any other method

CONCLUSIONS

- 1 Whole skin, sutured under tension as a buried graft, is an effective substitute for fascia in the repair of large herniae
- 2 There is little or no danger of the development of inclusion or retention cysts in these grafts
- 3 There is usually enough redundant skin over the hernia to provide for the graft The need for a secondary donor site seldom arises
- 4 The incidence of infection and hematoma formation is no greater than in other types of repair
- 5 This method can be used to correct some large herniae which would be very difficult to repair by any other type of procedure

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CIRSOID ANEURYSM OF THE SCALP REPORT OF A CASE*

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CIRSOID ANEURYSMS are discussed in the literature under various titles Virchow believed them to be tumors of blood vessels and called them racemose aneurysms Dupuytren considered them to be arterial varices, while according to Virchow, it was Breschet who suggested the term cirroid from the Greek *kirsos* meaning varix They are known also as arterial angiomas or aneurysms by anastomosis Reid in 1925 published an account of 33 cases of arteriovenous communications, including four cirroid aneurysms He made no distinction between the various types and used the term arteriovenous aneurysms to designate all conditions where abnormal communications between arteries and veins existed

Cirroid aneurysms of the scalp are rare In other parts of the body, the trauma leading to this lesion is most often a penetrating wound In the region of the skull, both intracranially and extracranially, the injury is usually a non-penetrating one A distinctive feature of cirroid aneurysms of the scalp is their progressive nature in contrast to the tendency toward stabilization often shown by similar lesions elsewhere in the body

It is now generally agreed that the cirroid aneurysm is a form of arteriovenous fistula in which the earliest abnormal communications are between the arterioles and the venules The inciting factor is believed to be trauma, frequently trivial, which results in rupture of the small vessels and brings about false communications between the smaller arteries and veins The ultimate effect of such abnormal openings is to divert blood under arterial pressure directly into the venous system with resultant venous dilatation The decreased resistance to the flow of blood from artery to vein at the site of the fistula as compared to the resistance to the flow of blood through the capillary bed elsewhere leads to an increase in the volume of blood flowing through the fistula and results in dilatation of all the vessels in the neighborhood The cirroid aneurysm comes to be composed essentially of two parts, the fistula itself and the dilated afferent and efferent vessels

There is a growing tendency in modern literature to disregard the term cirroid aneurysm and to discuss these lesions with other types of arteriovenous fistulas However, the term cirroid is so deeply entrenched in medical literature that its continued use seems justified Certainly the term has come to convey the clinical picture now familiar to all One need only recall that it is a type of arteriovenous aneurysm

A patient with a cirroid aneurysm of the scalp has recently been success-

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fully treated at the University of California Hospital. The case history and a brief discussion of the problem follow.

ARTERIOVENOUS ANEURYSM OF THE SCALP

F P, a 35-year-old white male, sustained a blow on the head resulting in a scalp laceration in an auto accident in February, 1942, 5 years before entering the University of California Hospital. The wound was immediately sutured and the patient had no further distress until $2\frac{1}{2}$ years later when he first noted swelling in the region of the previous injury. The mass steadily increased in size and the right temporal artery became

visibly enlarged and tortuous. For 2 months prior to admission he was aware of a "swishing" noise when reclining, more noticeable when the head was turned to the right side. He had noted that the noise was synchronous with his pulse.

At the time of entry there was a diffuse swelling which occupied the right fronto-parietal region of the scalp (Fig 1). This mass was composed of tortuous vascular channels extending posteriorly to the level of the external auditory meatus. The overlying skin was reddened, scarred and somewhat thinned out. The lesion was everywhere soft, compressible and non-tender. A continuous murmur with systolic accentuation was heard over it and a thrill could be palpated over its midportion. Both temporal vessels were dilated and tortuous. Compression of one or both of the temporal arteries decreased the size of the mass but did not obliterate it, nor was the bruit completely stilled. The optic fundi were normal and the auditory acuity was bilaterally equal. The remainder of the physical examination was not remarkable. There



FIG 1—The preoperative photograph demonstrates the diffuse nature of the aneurysm.

was no tachycardia and the heart was of normal size and shape. The pulse was not slowed by compression of the aneurysm.

In order to obtain arteriograms, the right common carotid artery, along with its internal and external divisions, was exposed under local anesthesia through an incision parallel to the anterior border of the sternomastoid muscle. While the internal carotid artery was temporarily occluded by a bull-dog clamp, 15 cc of 20 per cent thorotrast solution were injected into the external carotid artery. Thereafter, an injection of 25 cc of thorotrast solution was made into the internal carotid artery while the external division was occluded (Fig 2). A series of roentgen films was taken after each injection.

The intracranial circulation from the internal carotid artery appeared to be essentially normal. However, there was a channel, probably taking origin from the ophthalmic artery, which traversed the supraorbital region beneath the roof of the orbit and filled a vessel lying within the scalp (Fig 3A). The injection of the external carotid artery showed two large and tortuous arteries, one in the frontal and one in the parietal region (Fig 3B). The second film of the series showed filling of widely dilated tortuous channels which were presumably veins. The angioma received its main blood supply from the external carotid artery, although some of its supply came from the internal carotid artery through vessels which traversed the orbit just below the orbital roof.

CIRSOID ANEURYSM

Operation was performed under intratracheal nitrous oxide anesthesia. Bilateral incisions exposed greatly enlarged and tortuous temporal arteries along with their accompanying veins. Each temporal artery was divided and ligated (Fig 4, insert). A semi-circular fronto-parietal scalp incision was then made extending through the galea aponeurotica, and the entire scalp flap was reflected forward. The individual vessels were visualized and a large mass of tortuous, dilated and engorged arteries and veins was

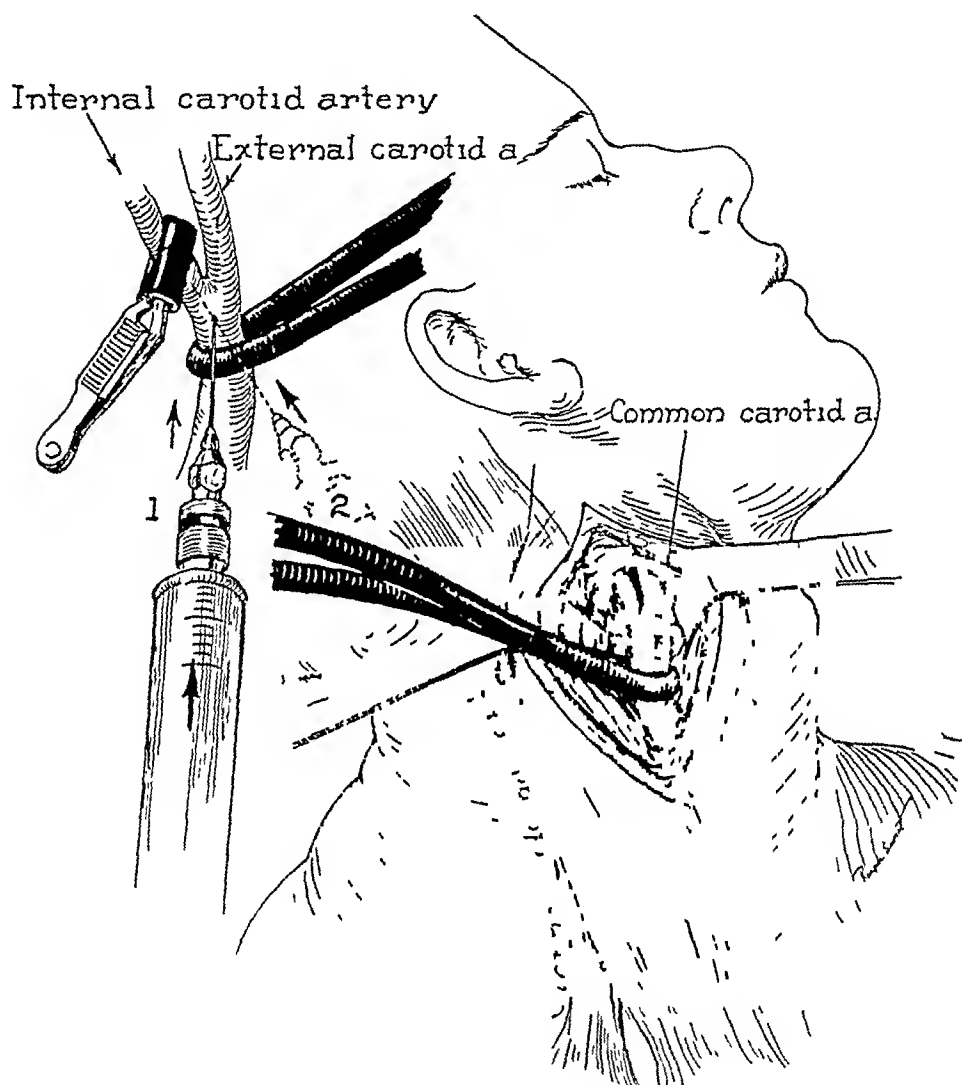


FIG 2—Angiograms of the aneurysm and its associated vasculature were obtained by injecting thorotrast into the external and internal carotid arteries

completely removed (Fig 4). The flap was replaced, sutured and held adherent to the skull by a firm pressure dressing.

The patient's postoperative course was uneventful and the wound healed *per primam*. There was no evidence of a bruit or thrill, and the patient was no longer conscious of the subjective noise noted before operation. All dilated and tortuous channels had apparently been removed (Fig 5).

DISCUSSION

Cirsoid aneurysms are most frequently traumatic, though sometimes they appear to arise independently through the presence of a pre-existing congenital

vascular abnormality of an angiomatous nature. They are considered to occur secondary to a congenital arterial angioma, or more rarely to a venous angioma. Although trauma is usually considered to be the inciting cause, some authors believe that inflammation plays a prominent role in their production.

Sites of predilection are the scalp, face, hands, and feet. Actually they may develop anywhere in the body, although there are few reports in the literature indicating the presence of cirroid aneurysms associated with the viscera. One such report concerns a cirroid aneurysm of the left gastric artery secondarily producing peptic erosion and copious gastric hemorrhage.



FIG 3 (A)—Roentgen film taken immediately after arterial injection, demonstrates the arterial supply of the aneurysm.

Clinically the aneurysm is easily diagnosed. It is a painless lesion even to firm palpation but causes distress because of the beating sensation of which the patient is constantly aware. Frequently intense headache and tinnitus may be experienced. Beneath the bluish tinged skin, the cirroid aneurysm appears as an irregular, diffuse, elevated mass which is not only soft but easily compressible. When pressure is released the mass quickly fills with blood and returns to its former size. There are usually visible pulsations, and a thrill synchronous with the arterial beat can be palpated. A blowing murmur can be

heard on auscultation over the aneurysm. This murmur may be continuous, continuous with systolic reinforcement, or biphasic with a strong systolic and a weaker diastolic component, or with simply a systolic one. Compression of the tumor causes disappearance of the murmur and thrill. The impression imparted to the examining hand is that of a mass of worms.

It is most important to determine the presence of communications with enlarged vessels within the skull. The injection of radiopaque material into



FIG 3 (B)—Roentgen film taken immediately after arterial injection, demonstrates the arterial supply of the aneurysm

the afferent arteries followed by an appropriate series of roentgen films will, in most instances, demonstrate the extent of the involvement.

The cirroid aneurysm is to be differentiated from an arteriovenous aneurysm and an angioma. The arteriovenous aneurysm affects the larger vessels and has but a single communicating fistula, pressure upon which causes the bruit or thrill to disappear. This phenomenon has been mentioned as Terrier's sign. In cirroid aneurysms, the communications are multiple, are between the smaller vessels, and the bruit or thrill disappears only when pressure is exerted

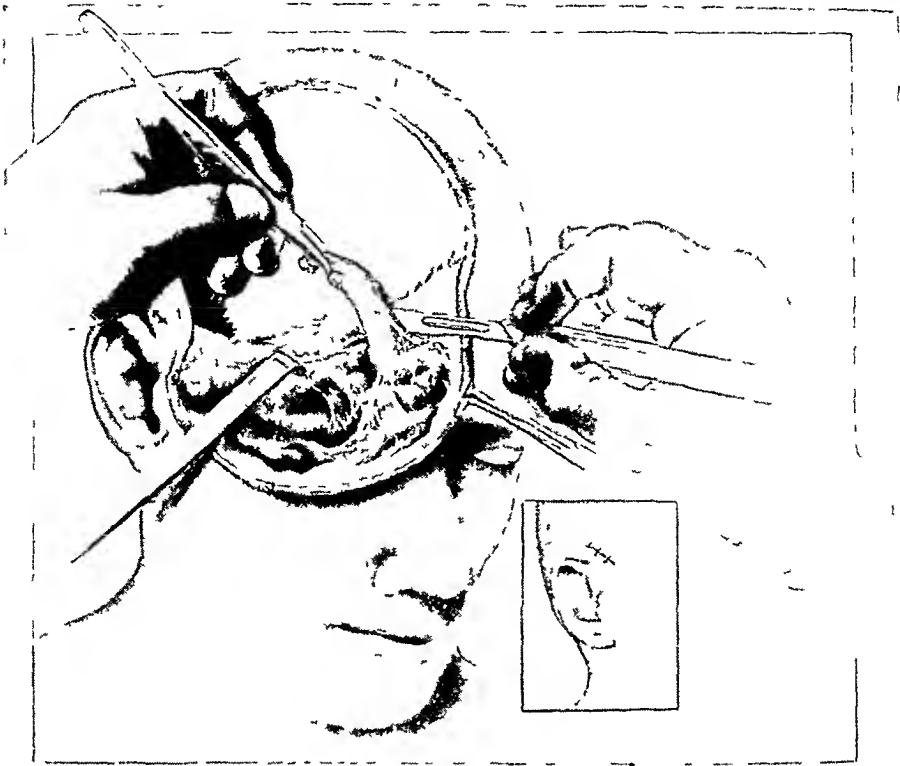


FIG 4—Diagrammatic representation of the operative procedure. Complete excision of the aneurysm was performed after preliminary ligation of both temporal arteries.



FIG 5—Two weeks after operation the wound had completely healed (A). The components of the aneurysm had been totally eradicated and the patient was no longer aware of the subjective "swishing noise" that he had noted before operation. The appearance of the operative area six months after surgery is shown in B.

over the entire surface of the tumor. Congenital angiomas appear as simple red or bluish areas over which there is no thrill, bruit or pulsation.

Most authors agree that cirsoid aneurysms never heal spontaneously. Various methods of treatment have been proposed. Among these are application of various caustic agents, injection of sclerosing solutions, compression, ligation of the afferent vessels, electrocoagulation, radiation and extirpation. Patey has recently described the successful use of arterial ligation combined with venous injection. The inefficiency of proximal arterial ligation as the sole means of treatment is well recognized. However, the value of preliminary ligation of the principal afferent artery or arteries at a point proximal to the lesion cannot be denied.

The most effective means of treatment is by complete surgical removal. In spite of all precautions this operation carries some risk from severe hemorrhage. Cirsoid aneurysms are cured by excising or eliminating by ligation the abnormal communications between arteries and veins. It is not always possible to ascertain the exact site of such fistulae. In order to be certain that all of them have been extirpated, it is frequently necessary to remove large masses of dilated vessels. If an abnormal opening is overlooked, some of the dilated vessels will persist. This phenomenon has led some observers to regard cirsoid aneurysms as neoplastic in origin. However, the evidence, both histologic and from follow-up studies, suggests that they are not neoplastic.

SUMMARY

Cirsoid aneurysms of the scalp are usually progressive in nature and result most frequently from non-penetrating trauma to an area containing a pre-existing vascular lesion of a congenital angiomatous nature. The cirsoid is a form of arteriovenous aneurysm exhibiting multiple abnormal communications between the smaller arteries and veins. The decreased resistance of blood flow through the multiple communications leads to a large volume flow of blood to the area resulting in a dilatation of all the vessels in the neighborhood of the fistula. The enlarged vessels are clearly visible and resemble a mass of worms beneath a thinned out and bluish tinted scalp. In contrast to the more common congenital angioma, the cirsoid aneurysm pulsates and exhibits a bruit and thrill over the abnormal communications.

Although many methods of treatment have been advocated, the procedure of choice is complete extirpation accompanied or preceded by ligation of the afferent arteries.

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PRIMARY SPLENIC NEUTROPENIA A SPECIFIC INDICATION FOR SPLENECTOMY*†

REPORT OF A CASE

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UNTIL RECENTLY, the conditions or diseases considered as an absolute indication for splenectomy were limited to traumatic rupture, idiopathic thrombocytopenic purpura, primary splenic anemia, and congenital hemolytic jaundice. In the past several years many diseases and entities have been added to this list. Recently included is a disease now known as primary splenic neutropenia.

Felty¹ was possibly the first to describe a condition or syndrome which was primarily a neutropenia, without any specific etiology, but which was associated with symptoms and findings of arthritis, skin manifestation, and splenomegaly. In 1924 he described and reported five cases. The condition was then named Felty's syndrome.

In 1932 Hanrahan and Miller² performed a splenectomy in a case of Felty's syndrome with complete alteration of the arthritis and return of the white blood count to normal. In the same year, Turley¹¹ suggested that the spleen destroyed polymorphonuclear leukocytes.

In 1939 Wiseman and Doan¹² reported three cases of leukolysis resulting in a specific granulopenic syndrome which they believed was due to splenic dysfunction and were cured by splenectomy. In 1942, when the same two authors¹³ reported five additional cases, the name primary splenic neutropenia was used to describe the syndrome or disease. At this time they reported what was believed to be a hitherto unrecognized cause of neutropenia, resulting from a pathologically altered, physiologic function of the spleen.

It is generally accepted at the present time that the spleen has three definite functions in the adult: (1) destruction of red blood cells, (2) production of lymphocytes, and (3) the storage of blood. Several authorities think the spleen performs other functions but these have not been definitely established.

The spleen may develop a selective destructive function of certain elements in the peripheral circulating blood, resulting in idiopathic thrombocytopenic purpura, if the platelets are destroyed, in hemolytic jaundice, if the erythrocytes are selected for destruction, and primary splenic neutropenia, if the leukocytes are the victims.

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Since the original descriptions of this unusual syndrome or disease characterized by a granulocytopenia, splenomegaly, and the ability of the bone marrow to function normally or show evidence of panhyperplasia very few cases have been reported in the literature ^{3 4, 5 6 7 12 13}

CASE REPORT

W G M, a white male, 50 years of age, admitted to the Medical Service March 22, 1944, at which time his chief complaints were Protruding bleeding hemorrhoids, fleeting joint pains, and occipital headaches. The joint pains began about one year before admission and shifted from one joint to another. At this admission his knee joints were causing some distress. The physical examination was negative except for protruding hemorrhoids and a scaly dermatitis of both legs which has been present for many years. Laboratory findings were negative. The patient did not have a blood count during this period of hospitalization. A hemorrhoidectomy was performed and was uneventful. The patient was discharged June 28, 1944.

He was readmitted to the Medical Service on Sept. 19, 1945, with complaints of pain in both shoulder joints, knee joint, and pain in the feet. He also complained of feeling below par, tired easily and became tremulous, nervous, and dizzy on slight exertion. The physical examination was essentially negative except for limitation of abduction of the arms to one-half of the normal range. A hyperkeratotic dermatitis was noted on both tibial areas of the legs.

On November 30, 1945, examination revealed the spleen to be palpable, three inches below the left costal arch. There was a small lymph node in the submental region and an inguinal node, 2 cm. in size, on the right side.

The patient during this period of hospitalization ran a remittent and intermittent low grade fever, never above 100° F. Roentgenograms of the spine revealed a mild hypertrophic lumbosacral arthritis. The most conspicuous findings were the changes in the white blood counts (Table I). On September 28, 1945, hemoglobin, 95 per cent, ery-

TABLE I--*Circulating Blood Picture--During Second Hospitalization*

Date	Erythrocytes	Hemoglobin	Leukocytes	Neutrophils
9-26-45	5 150 000	13.8 Gm	1 900	59
10-9-45	4 600 000	13 Gm	2 100	32
10-12-45	5 050 000	13.8 Gm	1 700	20
10-22-45	4 700 000	13 Gm	2 400	31
12-20-45		14 Gm	1 500	16
1-24-46	4 610,000	12.5 Gm	2 900	21
2-6-46			2 200	54
3-26-46	3 950 000	9.5 Gm	900	
4-24-46	3 300 000	10 Gm	1 700	
6-20-46	4 000 000		2 200	

throcytes, 5.15 M, with total leukocytes of 1,900, polys, 59 per cent, lymphocytes, 37 per cent, eosinophiles, 3 per cent, sedimentation rate, 5 mm. Sternal marrow biopsy was done and this revealed many mature erythrocytes, a rare nucleated cell and myeloblasts, 4, premyelocytes, 26, myelocytes, 8, band forms, 16, segmental neutrophils, 2, macroblasts, 44. The icterus index was normal. On November 30, 1945, a diagnosis was made of lymphatic leukemia in aleukemic phase. On the same date the patient was seen by the consultant in dermatology who made a diagnosis of lichen planus, lichen simplex chronicus or possible Boeck's sarcoid of the skin lesions of the legs.

A biopsy of skin was performed and on January 29, 1946, a diagnosis of lichen simplex was made.

PRIMARY SPLENIC NEUTROPENIA

The patient was treated by penicillin and pentnucleotides and was discharged from the Medical Service June 25, 1946

He was readmitted to the Medical Service on July 24, 1946, with the chief complaint of a painful, swollen area, anterior surface of left thigh. The area had been present for several days. Physical examination disclosed a swollen, reddened, tender area of left thigh, enlarged spleen, and palpable liver. The abscess of the thigh was incised, drained, and healed under penicillin therapy. The blood picture continued to show a normal erythrocyte count and hemoglobin value, and a leukopenia with low neutrophil count (Table II). Sternal punctures were performed and showed a normal sternal marrow with

TABLE II—*Circulating Blood Picture—During Third Hospitalization*

Date	Erythrocytes	Hemoglobin	Leukocytes	Neutrophils	Platelets
8-28-46	4 830 000	12 Gm	1 900	32	385,000
9-10-46	4 790 000	12.5 Gm	1 800		
10-7-46	5 250 000	14.0 Gm	2 500	62	
*12-3-46	5 400 000	12.5 Gm	14 400	94	
12-9-46	5 020 000	13.5 Gm	18 100	88	
12-16-46	4 710 000	12 Gm	13 100	72	
12-24-46	4 880 000	13.5 Gm	9 400	64	800 000
1-28-47	5 360 000	14.5 Gm	10 800	41	400 000

* Day following splenectomy

the ability of the marrow to form normal erythrocytes and leukocytes (Table III). The biopsy of the local inguinal lymph node showed fibrosis and no evidence of leukemia. On November 5, 1946, patient was seen by a consultant in medicine and hematology who stated that the patient had had a persistent leukopenia but has developed no anemia. Bone marrow examinations indicated that neutrophils were being formed properly so that their reduction in the peripheral blood must have been from too rapid destruction. The spleen was enlarged and obviously pathologic, and it was logical to assume that this was the site of excessive destruction. Leukemia was not probable because there was no anemia and it was not suggested in the bone marrow. He suggested biopsy of a lymph node to finally exclude lymphocytic leukemia. If this was excluded by the biopsy, he advised splenectomy.

TABLE III—*Sternal Puncture—Bone Marrow Studies*

8-26-46		10-9-46	
Segmented neutrophil	25	Bands	41
Band neutrophil	22	Metamyelocytes pmn	12
Metamyelocyte neutrophil	14	Myelocyte pmn	21
Metamyelocyte eosinophilic	1	Myelocyte eosinophil	7
Myelocyte	4	Premyelocytes	3
Promyelocyte	3	Blast cells	6
Blast cells	5	Lymphocytes	10
Lymphocytes	4		—
Megaloblasts	5	Total	100
Normoblasts	11		
Monocytes	1		
Unclassified	5		
Total	100		

The patient was seen in consultation by the Surgical Service on November 25, 1946, at which time the spleen was greatly enlarged and extended below the level of the umbilicus. The liver was not palpable and there was no evidence of ascites or anemia. The lymph node revealed fibrosis and the sternal marrow exhibited no abnormalities. A splenectomy was recommended and was accomplished on December 2, 1946, at which time the spleen was found to be greatly enlarged, occupying the entire left upper quadrant. The spleen was lobulated and the lower pole extended below the limit of the umbilicus. The spleen was so large and boggy that it was impossible to deliver it through the wound prior to isolating and dividing the splenic pedicle. There was, also, a small accessory

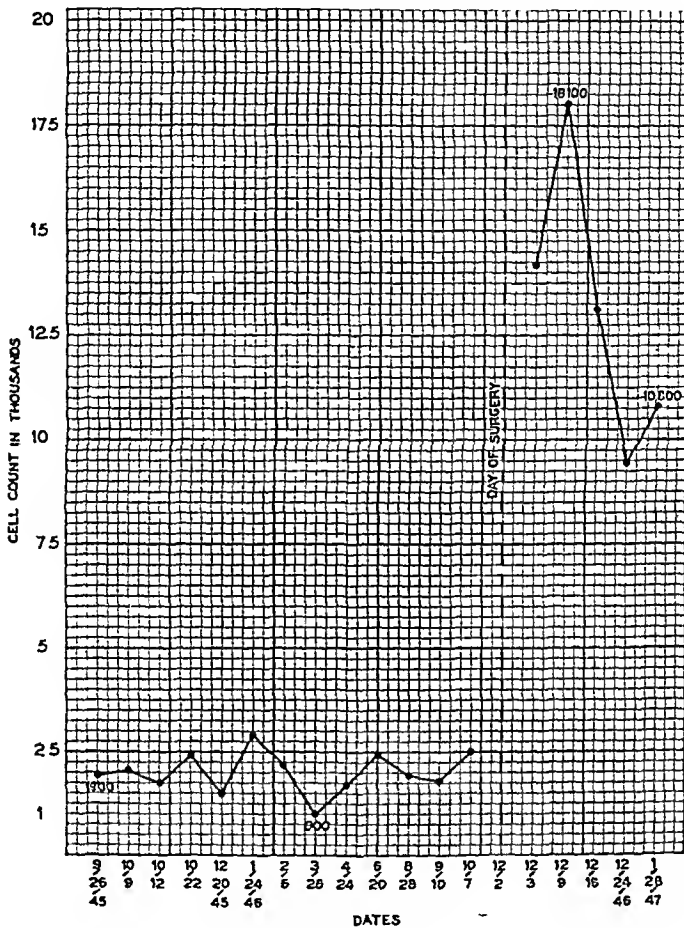


CHART I

White blood count prior to and following splenectomy

spleen which measured 1 cm in diameter, it was found near the hilus of the spleen. The liver was normal in size, color, and shape and its margins were smooth and sharp. There was no evidence of ascites or portal obstruction.

Prior to surgery the erythrocyte count and hemoglobin value were normal and the leukocytes revealed a persistent leukopenia varying from 1,400-2,500 (Table II).

The day following surgery the leukocyte count was elevated to 14,400 with 94 per cent polys and remained elevated during the remainder of the patient's stay in the hospital (Table III and Chart I).

The pathologist reported the specimen consisted of a spleen which was greatly enlarged and had a bluish discoloration. The discoloration was more marked in some areas where the capsule had been raised by hemorrhage. On the superior lateral aspect

PRIMARY SPLENIC NEUTROPENIA

of the spleen numerous small yellow plaques were impacted in the capsule, the average diameter being approximately 3 mm. One large plaque was found to measure approximately 1 cm in diameter. The specimen was very soft and the capsule was wrinkled. On cut section it was blood-red in color. There was considerable oozing of blood from the cut surfaces. The cut surface presented a speckled appearance, the specks being uniformly distributed and approximately 0.5 mm in diameter and of a bluish-white color.

A second specimen consisted of an accessory spleen, (1 cm in size).

Microscopic Examination The capsular surface was irregular but smooth. There was one nodule of symmetrically arranged fibrous tissue which revealed partial hyalinization. One area of subcapsular hemorrhage exhibited no hemolysis or organization and was apparently traumatic.

There was moderate dilatation of sinuses and mild reticulo-endothelial hyperplasia. Trabeculae were sharply defined and there was no fibrosis. Follicles were prominent and normal architecture was preserved. Arterioles revealed mild sclerosis. There was a small amount of pigment present which was not abnormal in amount. Sinusoids contained many mono- and multinucleated giant cells with oval nuclei and buff cytoplasm. Some contained small vacuoles and some contained nuclei of polymorphonuclear leukocytes.

The picture here presented was not typical of splenic anemia or Banti's syndrome, and it revealed no evidence of malignancy. It was compatible with the disease described as primary splenic neutropenia.

The patient made an uneventful recovery following surgery and was transferred back to the Medical Service on December 19, 1946, for further observation and follow up. The patient was discharged from the hospital on February 5, 1947, completely relieved of all symptoms, blood picture normal, and skin lesions completely healed.

CONCLUSIONS

1. A case of primary splenic neutropenia was presented as clinically cured by splenectomy and removal of an accessory spleen.

2. The case presented conforms to the description made by Wiseman and Doan in 1939 and 1942. The condition resembled Banti's Syndrome, Felty's Syndrome, subleukemic myeloid leukemia, hyperplastic anemia, malignant neutropenia, or certain types of chronic infection.

3. The disease results from a splenic dysfunction as a result of selective destructive action of the reticulo-endothelial cells of the spleen closely related to congenital hemolytic icterus and essential thrombocytopenic purpura in which cases the erythrocytes and platelets are destroyed respectively.

4. A definite and accurate diagnosis was dependent upon a complete clinical survey of the patient and a detailed study of sternal marrow, circulating blood, and biopsy of a lymph node.

5. This disease should be included in the long list of diseases in which splenectomy is definitely indicated.

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UNUSUAL METASTATIC MANIFESTATIONS OF BREAST CARCINOMA*

III METASTATIC INVOLVEMENT OF PREAURICULAR LYMPH NODES AND PAROTID GLAND A REPORT OF FIVE CASES

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ONE OF THE EARLIEST SITES for the appearance of metastatic mammary carcinoma is the ipsilateral axillary lymph nodes. Occasionally axillary node metastasis is discovered before the primary breast lesion is demonstrable.** Martin and Moir¹ found cervical node metastasis to be the first sign of breast carcinoma in 0.3 per cent of the breast cases reviewed by them. As the disease progresses the supraclavicular nodes may become invaded, the node situated behind the head of the clavicle in the sternocleidomastoid-clavicular angle is usually the first to become involved. This phenomenon is comparable to the appearance of the so-called sentinel node in advanced carcinoma of the stomach. The posterior cervical chain of nodes ultimately may become cancerous and in advanced cases of breast cancer node involvement may extend as high as the mastoid or occipital prominence.

It is however unusual for the preauricular lymph nodes or parotid gland to become invaded by the disease. The preauricular lymph nodes may be divided into three groups: (1) A superficial or supra fascial group which consists of one or two, occasionally three or four nodes situated in the neighborhood of the tragus. They are found in approximately one out of three individuals. (2) A subfascial group, containing one or two and occasionally three or four nodes, which lies between the fascia and the superficial surface of the parotid gland. These nodes are present in most individuals. (3) A deep intraglandular group composed of four to ten nodes situated in the areolar tissue which unites the superficial with the deep lobes of the parotid. These nodes are constantly present.

Three patients in whom the preauricular nodes and two in whom the parotid gland became involved secondary to carcinoma of the breast are reported in this communication.

Case 1—A W, a 37-year-old white woman underwent a left radical mastectomy in January, 1940, at the Memorial Hospital. The pathologic finding was an infiltrating duct carcinoma grade 3 metastatic to multiple axillary lymph nodes. The patient received postoperative roentgenotherapy to the left axilla and remained apparently free of disease for more than three years. A painful swelling then appeared over the upper left chest.

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** Report to be published.

near the sternal margin and a tiny node became palpable behind the head of the left clavicle. These were interpreted as metastatic disease and regressed with roentgenotherapy.

The patient remained asymptomatic for about seven months and then developed cough and dyspnea. Roentgenographic studies made of the chest at this time revealed evidence of pulmonary metastasis. On examination a firm, smooth, freely movable, painless subcutaneous nodule about one cm in diameter was palpated in the left preauricular region and was interpreted as metastatic involvement of a preauricular lymph node. An aspiration biopsy of this node was reported as carcinoma. No other nodes were palpable in the supraclavicular or cervical regions. The involved node in this case was one of the suprafascial group. The patient succumbed to the disease three months after the appearance of the preauricular node enlargement.

Case 2—A F, a 48-year-old white woman underwent a right radical mastectomy in 1940 at the Memorial Hospital. Pathologic examination revealed an infiltrating duct carcinoma grade 3 metastatic to one axillary node.

The patient remained apparently free of disease for about four years and then developed a bony prominence in the left parietal region of the skull with pain in the lumbar spine. Roentgen studies made at this time revealed evidence of metastasis to the ribs, lumbar spine, pelvis and skull. Radiation therapy was administered to the lumbar spine and pelvis with amelioration of the pain.

About six months later pain developed in the dorsal spine. Roentgenographic investigation revealed metastasis to the thoracic and lumbar spine with collapse of the body of the 6th dorsal vertebra. Several months later (about five years after her mastectomy) a smooth, firm, freely movable, non-tender, subcutaneous node about 1.0 cm in diameter was found in the left preauricular region. This was interpreted clinically as metastatic disease in a preauricular lymph node of the suprafascial group. There was no other external evidence of disease and no palpable adenopathy. The patient died of the disease about one month after the appearance of the preauricular node.

Case 3—L A, a 46-year-old white woman underwent a right radical mastectomy at the Montefiore Hospital in January, 1947. The pathologic report was undifferentiated carcinoma involving the pectoral muscles and metastatic to the axillary fat and lymph nodes. Roentgenograms of the lumbar spine and pelvis made before operation revealed no evidence of metastasis.

The patient was readmitted to the Montefiore Hospital three months later because of massive recurrence in the right anterior and posterior chest wall, right arm and anterior abdominal wall. There was no supraclavicular, cervical or right axillary adenopathy. One firm 2 cm node was palpable in the left axilla. The left breast was apparently normal. The liver was enlarged and nodular.

A subcutaneous nodule was noted in the right preauricular region about one month after admission. It was 2 cm in diameter, smooth, movable and non-tender, evidently suprafascial in location. Aspiration biopsy was reported as carcinoma. The patient died about two weeks after the preauricular node was discovered.

Case 4—J V, a 68-year-old white woman came to the Memorial Hospital in December, 1943, because of a painless lump in the right cheek of three months' duration. According to the patient the swelling was as large as a pea when first noticed by her and increased rapidly in size.

Examination revealed a 3 cm firm, well encapsulated mass in the right preauricular region which appeared to be embedded in the substance of the parotid gland (Fig 1). No lesions were noted in the oral cavity, pharynx or larynx. There were no palpable supraclavicular or cervical nodes. The general physical examination revealed a hypertension.

BREAST CARCINOMA

of 200/90 but nothing else of note. A diagnosis of mixed tumor of the parotid and hypertensive heart disease was made.

An aspiration biopsy of the tumor mass was reported as either lymphosarcoma or anaplastic carcinoma with the evidence favoring the latter diagnosis. To establish a definite diagnosis an excisional biopsy was performed. Dr. Fred Stewart's report and comment was "Adenocarcinoma grade 3. This may not be a primary parotid tumor. Is there anything in the breast?" This report prompted a reexamination of the patient's breasts. The findings were as follows: The breasts were small, symmetrical and the nipples normal. There was a slight fullness in the right breast on palpation. One small node was felt in the right axilla. On elevating the right breast a dimple was apparent in the inframammary sulcus (Fig 2). Palpation of this region disclosed a poorly defined, non-tender 3 cm mass. Aspiration biopsy of this lesion was reported as carcinoma. Roentgenograms of the lungs were negative for metastasis.



FIG 1

FIG 2

FIG 1 (Case 4)—The swelling in the parotid region is traversed by the scar of the biopsy incision.

FIG 2 (Case 4)—The retracted area is produced by the underlying breast carcinoma.

The face and breast lesions underwent considerable regression with roentgenotherapy. The patient has remained asymptomatic and there has been no evidence of activity of the neoplasm up to the present time—a period of four and one-half years. It is not possible in this case to determine whether the metastasis was to the parotid or to the intraglandular group of preauricular nodes.

Case 5—L. C., a 58-year-old white woman underwent a right radical mastectomy for advanced mammary carcinoma at another institution in September, 1943. She was asymptomatic for about three years and then developed pain in the cervical region, right arm and shoulder. Roentgenograms taken at this time revealed no abnormalities of the chest but there was destruction of the 6th cervical vertebra which was interpreted as metastasis. Despite roentgenotherapy pain in the right arm and shoulder continued and the patient gradually lost the function of this extremity.

In October, 1946, six weeks before admission to the Montefiore Hospital, a painless mass appeared suddenly in the right parotid region and increased rapidly in size. Exam-

mation on admission revealed a well-healed right radical mastectomy scar. There was paresis of the muscles of the right shoulder with motor and sensory loss in the right upper extremity probably due to involvement of the brachial plexus. A firm, non-tender, golf ball sized mass was found in the right parotid region (Fig 3). It was fixed to the underlying structures but the overlying skin was movable. There was no intra-oral lesion and no secretion could be expressed from Stenson's duct. No axillary, supraclavicular, cervical or inguinal nodes were palpable. Abdominal palpation revealed the liver to be enlarged and nodular. Roentgenological studies disclosed metastases to the skull, ribs, 5th, 6th and 7th cervical vertebrae and an area of destruction in the right mandible (Fig 4). A biopsy



FIG 3



FIG 4

FIG 3 (Case 5)—This reveals the diffuse enlargement of the parotid gland.
FIG 4 (Case 5)—A large defect involves the angle and ramus of the mandible.

of the parotid mass was reported as carcinoma. About one month after admission the patient became stuporous, probably from cerebral metastases, and she died shortly thereafter.

A postmortem examination revealed widespread metastatic mammary carcinoma. The right parotid gland appeared grossly to be extensively involved by grayish pink tumor tissue and histopathologic examination showed complete replacement of the gland by tumor. No parotid gland epithelium could be recognized. The angle of the right mandible was completely eroded, the defect in the cortex extending for 3 cm up the ramus and for 1 cm along the body of the mandible. Microscopic examination revealed necrotic tumor tissue replacing the marrow and invading the periosteum.

As in the preceding case it is impossible to determine whether the breast carcinoma metastasized primarily to the parotid or to the intraglandular preauricular nodes. Direct extension to the parotid from a mandibular metastasis is another possibility.

COMMENT

Each of our patients was in an advanced stage of the disease at the time that preauricular node or parotid gland involvement occurred and four of them died within a short time after invasion of these structures was observed. It

would seem that preauricular node or parotid gland metastasis is a late manifestation of mammary cancer

In two patients the involved preauricular node was on the same side as the breast lesion and in one patient (Case 2) it was on the contralateral side. Both patients with parotid gland metastasis had the involvement on the same side as the primary lesion of the breast. It is of interest that in no instance was there palpable evidence of supraclavicular or cervical adenopathy at the time the preauricular node or parotid gland became invaded except for one minute node behind the head of the clavicle in Case 1. The statement of Paget² in reference to bone metastasis that "some bones suffer more than others, the disease has its sites of election" may also apply to the sites of election of lymph node metastasis.

It has been shown in a previous communication³ that metastasis to the mandible from mammary carcinoma is an unusual occurrence. It is not possible to determine in Case 5 whether the mandible was involved by extension of the disease from the parotid gland or vice versa. It is possible that there was concurrent, independent involvement of mandible and gland.

Since the breast is one of the most frequent sites for the origin of cancer in women this organ should be suspected in instances of metastatic disease of obscure origin (Case 4). This case also illustrates the importance of elevating the breast and examining both visually and manually its under surface, a procedure which should be part of every routine breast examination.

SUMMARY AND CONCLUSIONS

1. Three cases of preauricular lymph node and two cases of parotid gland involvement by metastatic carcinoma of the breast are reported. Metastasis to these sites is of infrequent occurrence.

2. In one patient there was metastatic invasion of the mandible associated with parotid gland metastasis. In another patient the condition simulated a primary neoplasm of the parotid.

3. Preauricular node and parotid gland involvement are late metastatic manifestations of breast carcinoma.

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BRIDGING OF ESOPHAGEAL DEFECT BY PEDICLED FLAP OF LUNG TISSUE*

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GRAFTS OF LUNG TISSUE have been widely used for reinforcing sutures of the bronchial stump following lobectomy and pneumonectomy. In lobectomy, which as a rule is performed for benign lesions, preference is given to a pedicled flap. In pneumonectomy where the high level of bronchus dissection does not permit preservation of a pedicled flap, Churchill² was successful in securing the bronchial closure by a free graft of lung tissue taken from the periphery of the excised lung. The following case history will demonstrate that in surgery of the thoracic esophagus, lung tissue can be used for protecting critical areas in precisely the same way as omental grafts are used in abdominal surgery.

Case Report A 56-year-old male patient was admitted to the Israel Zion Hospital with a brief history of esophageal obstruction. Roentgenographs (Fig 1) revealed a half-moon shaped filling defect of the middle portion of the thoracic esophagus. Roentgenologic (Doctor Tolk) diagnosis was benign tumor, probably leiomyoma. Esophagoscopy (Doctor Silverstein) and biopsy revealed small ulcerations of the mucosa in the obstructed area. The impression of the endoscopist was also that of a submucous benign tumor.

At operation on June 20, 1947, the left thoracic cavity was entered through the bed of the 6th rib. A large tumor of the muscular sheath of the esophagus was found, extending from the inferior margin of the aortic arch to 2 inches below the level of the bifurcation. The tumor mass occupied the entire circumference of the esophagus. In order to expose and excise it, two segmental arteries arising from the descending aorta had to be severed. The muscle tube comprising the entire muscular wall of the esophagus was partly interwoven with and greatly thinned out by the tumor (Fig 2). In order to insure radical removal, the entire muscular tube was removed with the neoplasm. Great care was taken not to pierce the mucosa, although at two points (apparently the areas from which the biopsy was taken) the remaining mucosal layer was extremely thin. After completion of the excision there remained a mucosal cylinder 10 cm in length, deprived of its muscular sheath.

Since the vascular supply of this denuded area was probably insufficient because of the ligation of two segmental arteries and the scar formation in the mucosa, it was felt that the denuded area should be covered by viable tissue. Therefore, the adjacent upper segment of the lower lobe was mobilized and wrapped around this portion of the esophagus. A complete cover was thus obtained. The lung was fastened to the muscular sheath of the esophagus above and below the defect, in a manner demonstrated in the illustrations (Fig 3). The phrenic nerve was crushed above the diaphragm, a rubber catheter inserted through a separate stab wound in the 9th intercostal space and the incision of the chest wall closed in layers. Microscopic examination of the specimen (Fig 4) revealed leiomyoma.

Recovery was complicated by bronchitis and bronchopneumonia. There were at no time signs or symptoms of pleural or mediastinal infection. The intercostal drain was removed on the 3rd postoperative day and the sutures on the 10th day.

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BRIDGING ESOPHAGEAL DEFECT

The patient was fed parenterally for the first five postoperative days, after which time he was permitted to swallow small sips of water. On the 7th postoperative day soft food was allowed, and on the 10th postoperative day, solid food.

Esophagograms taken 3 weeks after the operation revealed a normal delineation of the esophagus, with some bulging in the area where the tumor was formerly located (Fig 5). This may have been due to the absence of the intrinsic esophageal musculature although the patient had no difficulty in swallowing.



FIG 1—Large defect of the middle portion of the thoracic esophagus

When seen 11 (eleven) months after operation the patient appeared to be in perfect condition. An esophagogram taken at this time was essentially the same as the previous one.

COMMENT The choice of operation in this case was between esophagectomy and the plastic procedure described above. Allowing the denuded and poorly vascularized mucosa to remain without proper protection was hazardous because of the possibility of necrosis and perforation.

Esophagectomy was deemed inadvisable for the following reasons:

1. The risk of the operation would have been out of proportion to the benign character of the lesion.

2 Roentgen-ray pictures taken previous to the operation revealed a rather short stomach. It seemed questionable whether the entire length of the thoracic esophagus could be replaced by the mobilized stomach.

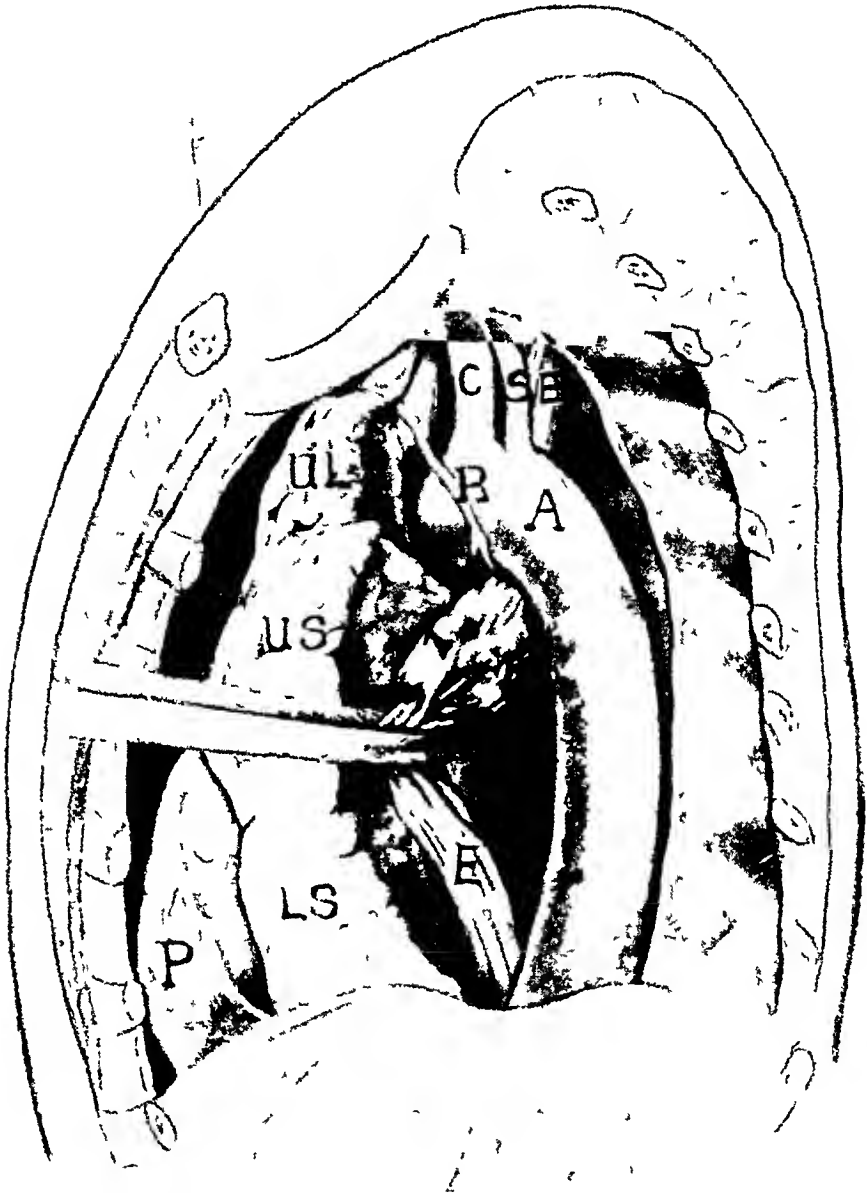


FIG 2—Sketch of the leiomyoma in situ

- | | |
|--------------------------------|----------------------------------|
| A Aorta | LS Lower Segment of Lower Lobe |
| R Recurrent Laryngeal Nerve | P Pericardium with Phrenic Nerve |
| UL Upper Lobe | E Esophagus |
| US Upper Segment of Lower Lobe | C Arteria Carotis comm sin |
| | S Arteria Subclavia sin |

3 Intrathoracic displacement of the partly devascularized and denervated stomach is followed by well known functional disorders. These may

BRIDGING ESOPHAGEAL DEFECT

be disregarded in the presence of a carcinoma, but should be taken into account if removal of a benign lesion is planned

In muscular or mucosal defects of the *lower* esophagus conditions are different. A pedicled flap taken from the diaphragm or a pedicled omental graft



FIG 3—Sketch of the operative procedure. The denuded portion of the esophagus is covered by a pedicled flap of the upper segment of the lower lobe of the left lung



FIG 4—Photography of the specimen

brought into the thoracic cavity through a small transdiaphragmatic laparotomy can be used to reinforce the esophageal wall. Excision of the lower esophagus, which is less hazardous than total esophagectomy may be considered in these cases. However, out of three cases of resection of the lower

esophagus for myoma of the cardio-esophageal region (S W Harrington and H J Moersch, B Dick⁷ and R C Brock¹), two died from pulmonary complications. Only Brock's case survived.

Simple excision of a leiomyoma of the lower esophagus was first performed by Sauerbruch⁵ in 1932. At operation an accidental tear was made into the mucosa. Since closure of this opening by two layers of sutures would have effected narrowing of the lumen, Sauerbruch made use of the opening in adding an esophagogastrostomy. Additional cases of excision were reported



FIG 5—Esophagogram taken 3 weeks after the operation

by T Ohsawat⁴ in 1933 and by P W Schaefer and C F Kittle⁶ in 1947. Schaefer and Kittle found it "necessary to excise an ovoid portion of the left posterolateral wall measuring 3 by 7 cm. This defect was closed longitudinally by two rows of interrupted O chromic catgut sutures." In these patients, where simple excision of leiomyoma of the lower esophagus was performed, recovery was uneventful.

Our case appears to be the first surgically treated leiomyoma of the middle portion of the esophagus.

BRIDGING ESOPHAGEAL DEFECT

SUMMARY

An extensive muscular defect of the middle portion of the thoracic esophagus was covered by pedicled flap of lung tissue

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RUPTURE OF A SUBPHRENIC ABSCESS INTO THE PERICARDIUM*

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DIRECT EXTENSION OF a subphrenic abscess through a perforation in the diaphragm into the pleural cavity or lung is not uncommon, but a similar extension into the pericardial sac is apparently rare. The following case is presented because of its rarity and because it illustrates the occasional undesirable masking of deep seated suppurative processes by antibiotic and chemotherapeutic drugs.

CASE REPORT

First Admission A S, a 35-year-old, single white male was admitted to Kings County Hospital on October 9, 1946, with a ten-year story of symptoms compatible with gastro-duodenal ulceration and a recent sudden attack of severe epigastric pain. The clinical picture was that of a perforated peptic ulcer, and a celiotomy was performed 9 hours after the onset of symptoms. There were found a generalized acute peritonitis, a moderate amount of cloudy fluid in the abdominal cavity and a perforation 7 mm in diameter on the anterior aspect of the first portion of the duodenum. An attached tab of lesser omental fat was placed into the perforation and held there with three silk sutures. The latter penetrated all layers of the bowel, which has been the usual method of closing large ulcers on this service. As much as possible of the free fluid was aspirated from the abdomen and the wound was closed without drainage.

The postoperative course was stormy and consisted of the following pertinent features. There was abdominal distention for the first 14 postoperative days. A rectal examination on the 12th day revealed a pelvic mass. A roentgenogram of the chest on the 28th postoperative day demonstrated a moderate pleural effusion at the left base and subillumination of the lower lung field on the right side. Four weeks later a second roentgenogram revealed almost complete resolution of the pleural effusion as previously observed. The temperature varied from 100° F to 101° F for the first 28 days, but had subsided to normal by the 33rd day and remained so thereafter.

In addition to the usual supportive measures the patient was given 3,520,000 units of penicillin during the first 12 days, and 4,800,000 units of penicillin and 132 Gm of sulfadiazine from the 28th to the 48th postoperative day. The penicillin was given intramuscularly in doses from 30,000 to 50,000 units every 3 hours, and the sulfadiazine was administered by mouth, 1 Gm every 4 hours. Fifty-one days after operation the white blood count was normal whereas it had been elevated during the period of pyrexia. At this time a rectal examination revealed the pelvic mass to have resolved into a small, non-tender, hard nodulation. On the 58th day following operation the patient was discharged to the Out-Patient Department feeling well. Subsequently, he was seen twice and complained of no symptoms relative to the ulcer, the operation or sequelae thereof.

Second Admission The patient was readmitted to the hospital at 12 00 noon on January 30th, 1947, because of severe chest pain. Nine hours prior to admission he was awakened with a severe pain in the back at the level of the scapulae. The pain, which

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SUBPHRENIC ABSCESS

was slightly worse to the left of the midline, was steady and continuous. There was also noted a less severe, diffuse, sticking pain across the lower chest anteriorly. This was moderately exaggerated by deep respirations. Vomiting of clear fluid occurred several times. During the week prior to admission he had felt feverish, but there were no chills, and no abdominal pain.

Physical Examination The patient was alert and cooperative, but acutely ill and apprehensive. There was moderate dilatation of the neck veins and a somewhat dusky red color to the skin of the upper chest and neck, but no pallor, cyanosis or jaundice were observed. The pulse rate was 144 per minute and regular. The respiratory rate was 36, temperature 105.8° F and the blood pressure was unobtainable. The findings pertaining to the lungs were not remarkable except for an area of increased whispered pectoriloquy and bronchial breathing in the right mid-chest posteriorly. This was not heard several hours later. The heart tones were normal but weak. The abdomen was flat, soft and not tender. The old operative scar was well healed, no masses were felt and the bowel sounds were normal. Digital rectal examination revealed the same findings as upon discharge, 8 weeks before. The white blood count was 12,000 with 66 per cent polymorphonuclear leukocytes.

A plain film of the abdomen demonstrated irregular distention of small bowel and some gas within the stomach. An upright two meter chest film revealed no evidence of recent pulmonary or pleural disease. There were, however, minimal thickening of the pleura at both apical regions and a few fibrotic deposits in the superior portion of the right hilum. There was no free air under the diaphragm. The cardiac contour was within normal limits.

General supportive and symptomatic treatment was instituted without beneficial response. Aspiration of the stomach yielded 500 cc of light yellow fluid. During the afternoon the Trendelenburg position was instituted in an attempt to mitigate the vascular collapse, but it had to be discontinued because the clinical picture became even more alarming. The course was rapidly downhill and 8 hours after admission the pulse was no longer obtainable. Death occurred at 10 00 p m., 10 hours after admission and 19 hours after the onset of symptoms.

Necropsy Examination of the abdominal cavity revealed the spleen to be fixed in position by old fibrous adhesions and there were numerous intestinal adhesions, especially in the pelvis. There was no duodenal ulcer and the site of previous repair could not be identified by either gross cicatrix or the presence of sutures. To the left of the coronary and falciform ligaments, on the superior and anterior surface of the left lobe of the liver there was an abscess cavity which extended into and through a necrotic portion of the diaphragm. The cavity, which measured 2 cm in diameter, had a thick fibrous wall. The abscess did not invade the liver substance nor did it communicate with the pleural sac. The abscess cavity was continuous, however, through a 2.5 mm perforation in the diaphragm, with the pericardial sac. The latter contained about 350 cc of grayish yellow pus and many recent fibrinous adhesions. The heart and great vessels were otherwise normal. Cultures of the pus from the abscess cavity grew hemolytic *staphylococcus aureus* and *escherichia coli*. Death was believed to have been caused by a fulminating suppurative pericarditis and cardiac tamponade.

COMMENT

In a limited review of the literature one other case of direct extension into the pericardium of a subphrenic abscess complicating a gastroduodenal perforation was found. Graves,¹ in 1863, described the perforation into the pericardial sac of an "hepatic" abscess, which was in direct continuity with the lumen of the stomach through a perforated gastric ulcer. Several cases of rupture of a gastric ulcer directly into the pericardium or heart itself have

been recorded.^{4, 5} Cabot⁴ reported one case of a pericardial perforation by a subphrenic abscess following biliary tract disease. Numerous writers have recorded isolated cases wherein an amoebic abscess of the liver extended into the subphrenic space and finally eroded through the diaphragm into the pericardial sac.^{5, 6, 7, 8, 9, 10} The latter condition is also discussed in various texts on tropical diseases.^{11, 12, 13} This complication is very rare, however, because it has always followed an abscess in the left hepatic lobe, which in itself is uncommon.¹³

In none of the reported cases reviewed, except those with pneumopericardium, was the diagnosis made clinically. To make this diagnosis Fontan¹⁴ has stated that one must have "an apprehensive patient complaining of left scapular, precordial and epigastric pain, decreased heart tones, a pericardial friction rub, and a sagacious observer." The clinical picture of acute pericarditis is not unlike that of myocardial infarction and the latter was considered in the differential diagnosis of the presented case. If one thinks of pericarditis however, the differential diagnosis can be made, as has been adequately discussed elsewhere.^{14, 15} When there are superimposed the signs of cardiac tamponade, *i e*, a "very weak heart," venous and capillary engorgement of the upper chest and neck, and aggravation of symptoms by the Trendelenburg position, the diagnosis should become apparent, especially in a patient with a history of antecedent subphrenic inflammation. When air is present in the pericardial sac the physical findings are unique. These have been recently discussed by H. Willy Meyer.¹⁶ In retrospect, it is believed that the diagnosis should have been strongly suspected in the presented case and that an exploratory pericardiotomy was indicated. Possibly this would have been life saving.

Another factor which may have altered the end result was the use of antibiotic and chemotherapeutic drugs in an attempt to control the infection during the first admission. Ochsner and Graves¹⁷ and Ochsner and DeBakey¹⁸ have stated that the majority of subphrenic "infections" subside spontaneously. Furthermore it has been postulated from bacteriologic studies,¹⁹ that the use of chemotherapy should reduce the mortality of gastroduodenal perforation. In this case, a subphrenic abscess was suspected on the 28th postoperative day. The seemingly satisfactory clinical response to penicillin and sulfadiazine masked the underlying suppurative process, therefore surgical exploration was no longer entertained. If these drugs had not been used the abscess probably would have been evacuated surgically, thereby obviating the lethal sequelae. It is suggested that in the future one must continue to be watchful for occult abscesses even though the patient apparently responds well to chemotherapy as evidenced by the usual clinical signs.

Thanks is expressed to Dr. Phillips F. Greene, Associate Dean, Long Island College of Medicine, for his aid in accumulating the bibliography.

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INTRAPAROTID SEBACEOUS GLANDS*

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THE ORIGIN OF MIXED TUMORS of the salivary glands has been disputed since the tumor was first described about 95 years ago. The term "mixed tumor" is based on the presence in such tumors of parenchymal tissues which are morphologically epithelial, and a chondromyxomatous stroma, the appearance of which indicates a mesodermal origin. Until fairly recently the controversy centered primarily in the conception that the tumors must arise in either one germ layer or the other—that they must be either mesothelial or epithelial in origin. One school advanced the theory that they might be endothelial in origin. Paget, Virchow, Billroth, Robin and others contributed to the literature of the subject in their time. More recently Ewing maintained that the tumors are derived from salivary epithelium which, retaining the power to secrete ptyalin and mucus, transforms the collagenous connective tissue stroma into mucoid tissue and finally into cartilage or pseudo-cartilage.¹ However, since new growths morphologically similar to mixed tumors of the salivary glands occur in the skin, mucous membranes, lungs, and in glands other than the salivary glands (such as the breast) the action of ptyalin and mucus secreting cells in producing them is not an entirely satisfactory explanation.

The various theories regarding these tumors have been summarized by Hemplemann and Womack² who have studied the tumors exhaustively by histochemical methods. Using techniques first developed by Hemplemann they were able to demonstrate specific mesenchymal and epithelial mucoids or mucoproteins and conclude that both basic tissues contribute to the development of mixed tumors. Their work offers strong confirmation of this conception which has been expressed by many recent writers and they point out that "In line with embryologic evidence, the buccal ectoderm of the salivary gland anlage probably affects the surrounding buccal mesoderm. In turn, the differentiation and development of the ectoderm is probably influenced by the buccal mesoderm."

Ramsay,³ in discussing a constant epithelial rest known as the "Organ of Chievitz" arising in close relation to the embryonic parotid gland comments that "the ultimate fate of such an epithelial structure which becomes embedded in the surrounding tissue (mesenchyme) rests upon the early vascular and mechanical relations into which it is introduced. If favorable conditions are met in the developmental epoch of such an "inclusion" its fate might be quite different from that of a non-adaptive and passive existence."

A case recently seen in this Clinic is of some interest in this connection

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INTRAPAROTID SEBACEOUS GLANDS

CASE REPORT

The patient, B. H., was a 15-year-old boy who came to the Clinic December 27, 1947, complaining of an unsightly tumor on the left side of the face, just in front of the left ear. He had first observed it about a month previously. It had always been entirely painless and had grown very little since he first noticed it. He suffered from a rather severe acne vulgaris of the face, neck and shoulders and there was obvious overactivity of the sebaceous glands of his skin. He had thought that the lesion was a "wen" and paid little attention to it until it gradually became large enough to become unsightly.

Examination showed a hard, non-tender tumor 1.0 cm in diameter about 2 cm

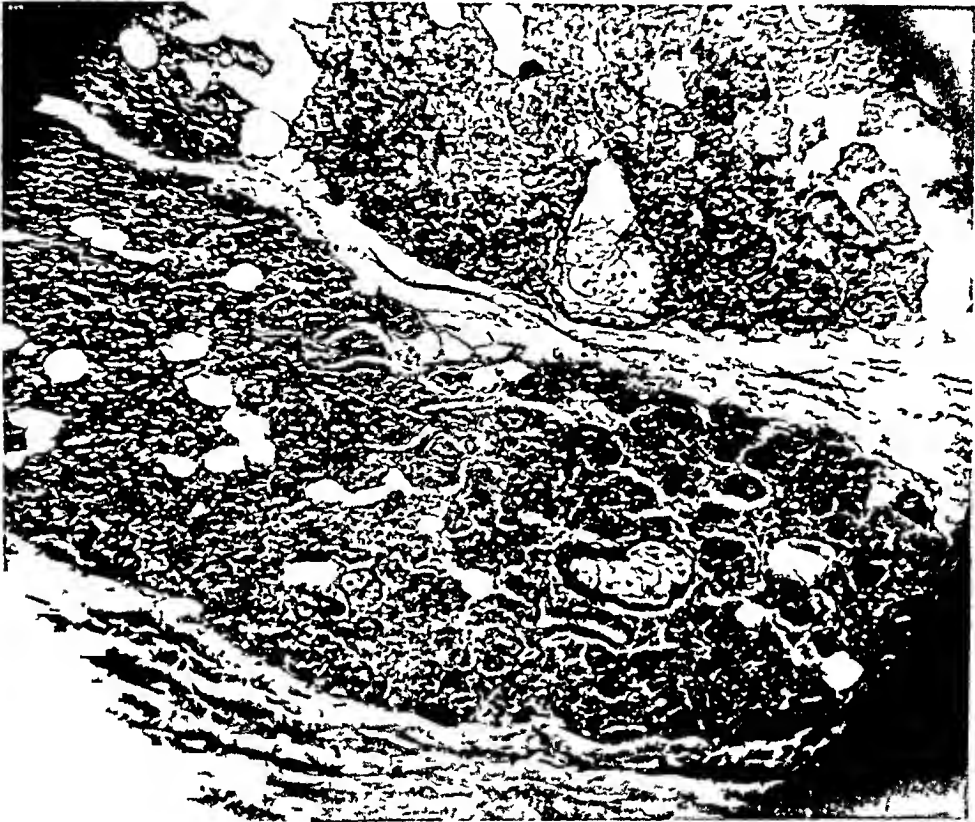


FIG 1—Photomicrograph of a section of the parotid gland showing well differentiated sebaceous glands within the parenchyma. These heterotopic glands were quite numerous, but rather widely scattered so that only two are seen in the illustration.

anterior to the tragus of the left ear. The skin was not adherent over any part of the lesion and palpation suggested that it lay in the parotid gland. There were numerous acne pustules and scars over the face and forehead and small sebaceous cysts about the ear.

The following day the tumor was removed under local anesthesia under a diagnosis of mixed tumor of the parotid gland. It was found to lie within the parenchyma of the gland, and although it was well encapsulated and was dissected out, a portion of the overlying parotid gland was removed with it. The wound healed uneventfully and the sutures were removed on the fourth postoperative day. There has been no recurrence to date (six months). Grossly the tumor was compatible with a mixed tumor. On microscopic examination, however, the main tumor mass proved to be the parotid lymph node in a state of hyperplasia. Interest centered in the fragment of parotid gland which had been removed with it. Scattered through the gland parenchyma were numerous heterotopic sebaceous glands (Figs 1 and 2). These sebaceous glands were multiple and well differentiated and scattered diffusely through a considerable portion of the section. In

some the appearance of the glands suggested that they might be developing from intra-lobular ducts of the parotid gland, although this appearance might be attributed to the angle and level through which the section chanced to pass. There was a diffuse round cell infiltration of the parotid gland itself suggesting a chronic inflammatory process.

Only one comparable case has been discovered in a review of the available literature. This was reported by Hartz⁴ in 1946 and he had been unable to find a similar case in the literature up to that time. Ramsay⁵ states that the parotid anlage arises from the sulcus buccalis just back of the angle of the mouth after a certain amount of reduction in the oral cleft has taken place.



FIG 2—Higher magnification of one of the sebaceous glands seen in Figure 1

giving opportunity for inclusion in the parotid bud of internally displaced epidermal material. For this reason the parotid gland would be expected to contain such elements as this case shows, in much greater frequency than would the organ of Chievitz since the latter arises from the buccal sulcus deeper (internally) than the parotid.

Moorhead,⁶ in presenting a series of mixed tumors of the skin, supports the now widely accepted view that mixed tumors arising in the skin, breast, salivary glands and other tissues are histogenetically similar. He believes⁷ that "mixed tumors—arise from pluripotential misplaced ectodermal cells which under proper conditions exert their property to differentiate into various structures normally derived from ectoderm." The connective tissue differen-

tations, that is the chondromyxomatous stroma, would correspondingly arise from the provocative action of abnormal connective tissue cells

COMMENT

It would appear from the evidence here presented that well differentiated heterotopic holocrine glands probably appear in the otherwise normal salivary gland more often than would generally be suspected. That they have escaped attention is probably due to the fact that biopsy of the gland, except in cases of existing tumors is seldom indicated. If such is the case, the presence of these structures lends support to the opinion expressed by Moorhead that "mixed tumors of the skin the salivary glands and the breast arise from abnormal epithelial cells which have similar developmental potentialities and which exert a provocative action on the mesoderm, resulting in the formation of heterotopic tissues of various types."

SUMMARY

A case is presented in which multiple well differentiated sebaceous glands are demonstrated within the parenchyma of the parotid gland.

The possible relationship of such structures to the origin of so-called "mixed tumors" is suggested.

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CERTAIN ANATOMIC FACTORS RELATED TO THE PATHOGENESIS OF HEMORRHOIDS*

THE AUTHOR'S "OBLITERATIVE SUTURE" IN THE TREATMENT OF THE
SMALL AND MIDDLE-SIZED INTERNAL HEMORRHOIDS*

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BY DEFINITION, hemorrhoids are venous dilatations or varices of the veins of the lower rectum and the anal canal. The appearance of this varicose condition seems to be closely related to the following six anatomic factors, existing in the anorectal region:

1 Absence of venous valves and lack of muscular or fascial support of the hemorrhoidal plexus

2 Extreme looseness of the sub-mucous connective tissue rendering the effect of gravity particularly harmful in the sitting and standing postures. It is noteworthy that quadrupeds are almost free from hemorrhoids, as in them this region does not suffer from the results of gravity.

3 The passage of the tributaries of the superior hemorrhoidal vein directly through the muscular wall of the rectum (See Figs No 1 and 2) about $7\frac{1}{2}$ cm above the anus, causing intermittent constriction of the veins at that point.

4 The communication of the superior hemorrhoidal vein (carrying most of the blood) with the inferior mesenteric vein, and thus with the portal system, which is subject to periodic physiologic congestion (as during digestion) and to frequent pathologic obstructions (liver cirrhosis, abdominal tumors, pregnancies, and other causes leading to portal hypertension).

5 The plexiform anastomoses just within the anus between the inferior and middle and the superior hemorrhoidal tributaries so that the former, although connected with the systemic circulation are subject to dilatation as result of portal congestion.

6 The relation of the hemorrhoidal veins and of the terminal branches of the inferior mesenteric veins to the fecal contents of the sigmoid and rectum exposing them to frequent pressure.

In evaluating the above six anatomic factors, one cannot help but attach most significance, as far as the pathogenesis of hemorrhoids from an anatomic point of view is concerned, to the lack of fascial support of the veins and to the looseness of the submucous connective tissue of the anorectal region.

The other factors follow closely, adding each one of them their weight to the appearance of the anal varicosities.

From the above, one may rightfully conclude that at least small and medium-sized internal hemorrhoids, especially the flat variety, could be treated effec-

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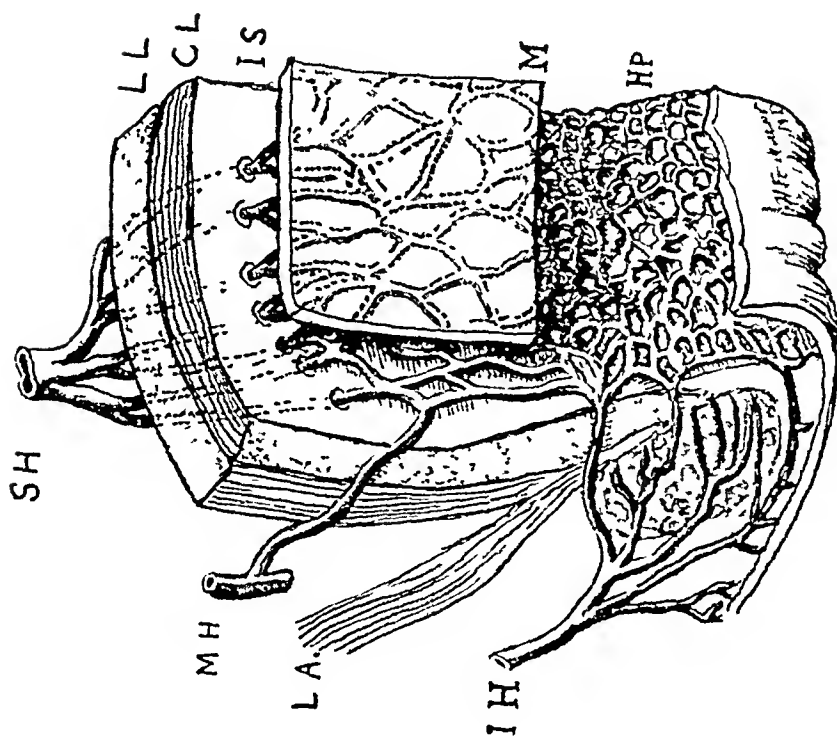


Fig 1—Schematic drawing showing normal hemorrhoidal plexus (HP) formed by the anastomosis of the superior (SH), middle (MH), and inferior hemorrhoidal veins. The extreme looseness of the submucosa is represented by the distance between the mucosa (M) and the internal sphincter (IS).
L.A.—Levator ani muscle LL—Longitudinal muscular layer of the rectum CL—Circular muscular layer (Redrawn from F. Paire, S. Dupret)

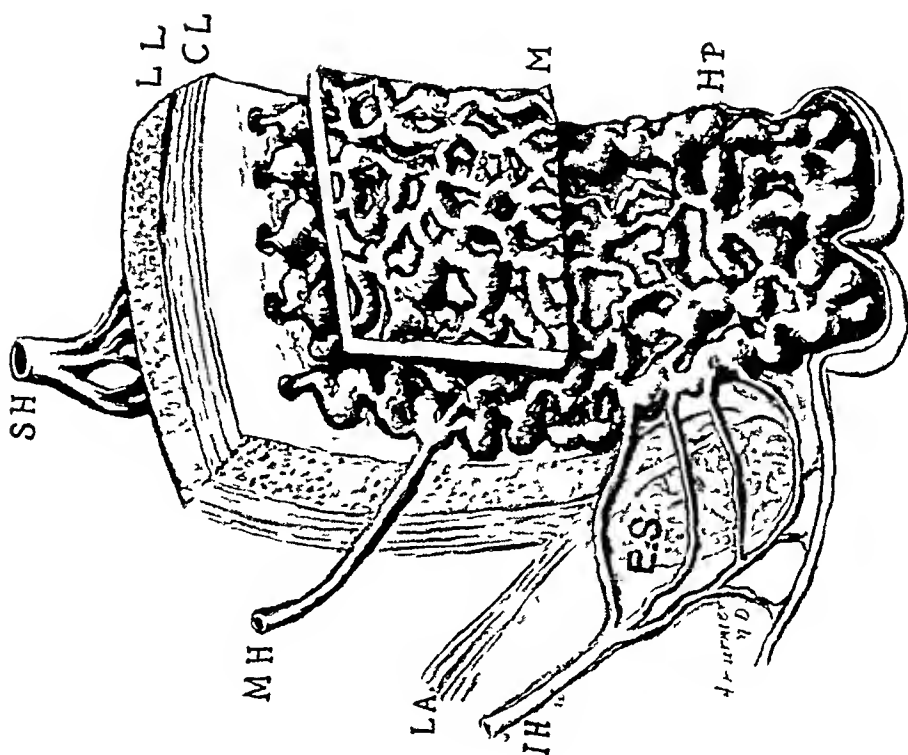


Fig 2—The anorectal region showing, as in Fig 1, the formation of varicosities (internal-external hemorrhoids). Legend same as in Fig 1

tively by a continuous or interrupted "obliterative suture" (double o chromic catgut), which embracing all the dilated veins (See Figs No 4 and 5), not only "obliterates" them but fixes them as well through the production of dense connective tissue to the rectal wall

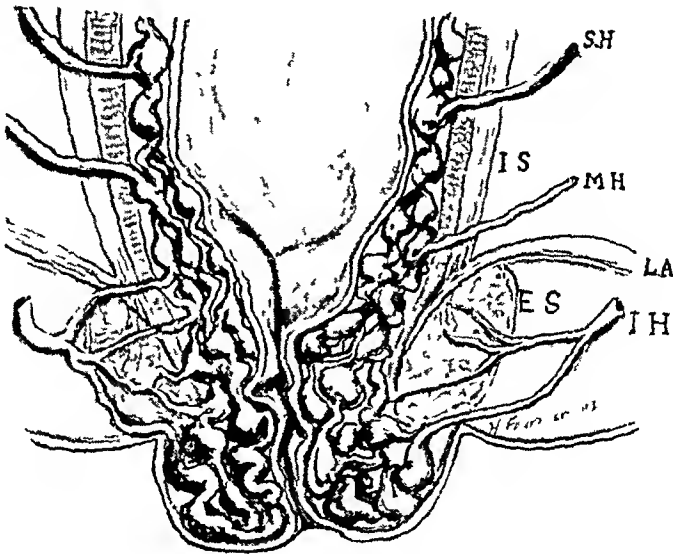


FIG 3—Frontal section of the rectum showing the development of hemorrhoids in an extremely loose submucosa (Legends same as in Fig 1)

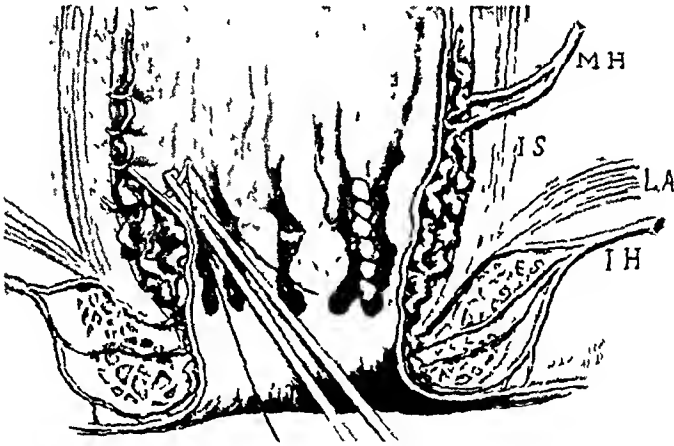


FIG 4—Frontal section of the rectum showing the application of the "Obliterative Suture" which at the same time is a fixative one. Note the simplicity of its application and the good results in collapsing the varicose veins and fixing the mucosa to the muscular layer

This "obliterative suture" simplifies astonishingly the treatment of those hemorrhoids, which could not be easily clamped, excised, and ligated, due to their diminution during the dilatation of the rectum with rectal retractors

Equally amenable to this treatment are those internal hemorrhoids that lie between excised and ligated masses where one hesitates to remove any more rectal mucosa for fear of undue trauma and hemorrhage

PATHOGENESIS OF HEMORRHOIDS

Figures 4 and 5 show in a semi-schematic way how the anorectal region would look after the application of this "obliterative suture"

TECHNIC

After the hemorrhoidal mass has been identified, one starts suturing its upper part (using an atraumatic curved needle, threaded with double 0 chromic catgut) transfixing its entire thickness by passing the needle from side to side

In so doing, the needle should go deep enough to embrace slightly the muscular coat of the rectum so that, when one tightens the thread over the mass, the entire hemorrhoidal plexus of that area should be obliterated and fixed to the rectal wall

After this first suture, which serves for anchorage, one proceeds to suture the entire mass in a continuous fashion, using the same needle threaded with

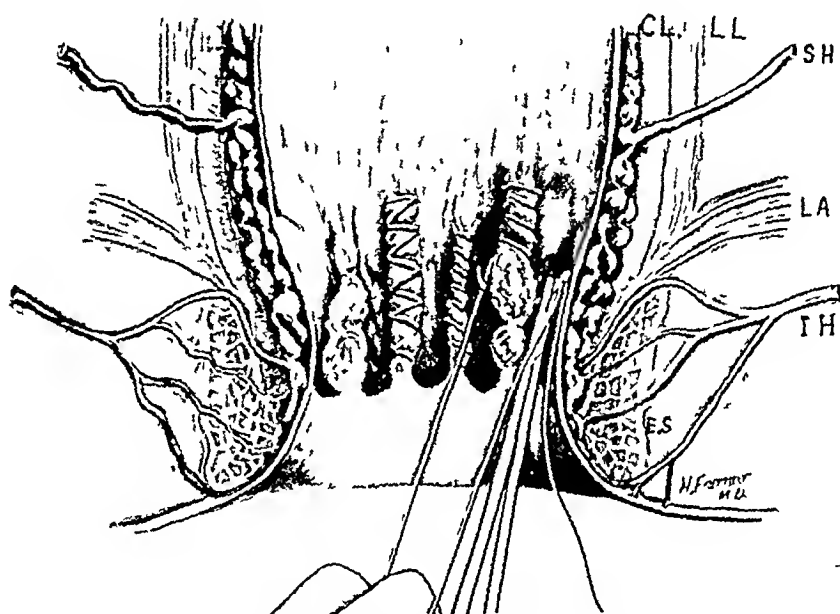


FIG 5—Showing the application of the "Obliterative Suture" in three hemorrhoidal masses. One hemorrhoid is still in process of being obliterated and fixed

the same catgut. The needle should pass from side to side as was done in the beginning of the suture and the distance between the following ones (usually 3-4 mm) should be such as to allow a complete "obliteration" of the entire hemorrhoidal mass after tightening the thread (See Figs 4 and 5)

One should end this continuous suture at this point, making a knot with the thread or if one wishes to add more secure "obliteration" one may continue in an ascending fashion to reach the starting point, where the thread is secured and its ends cut (See again Figs 4 and 5)

SUMMARY

Certain anatomic factors have been mentioned which are related to the pathogenesis of anorectal varicosities and an "obliterative suture" has been proposed to deal with small and medium-sized internal hemorrhoids. This

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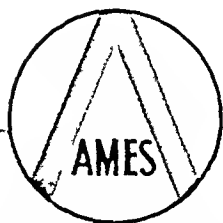
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FEBRUARY, 1949

No 2



EXPERIMENTAL RECONSTRUCTION OF CARDIAC VALVES BY VENOUS AND PERICARDIAL GRAFTS*†

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RECENT DEVELOPMENTS in the surgical treatment of congenital cardiovascular disease^{6, 11, 20, 21, 29} and in improving the blood supply to the heart by operative means^{3, 18, 44} have stimulated interest in the surgical attack on other cardiac lesions. Despite the recent report of successful incision of a stenotic valve by Smithy,³⁸ and the method of closure of septal defects described by Murray,²⁶ it seems to us that effective surgical therapy of most intracardiac lesions will require operation under direct vision. This is not practical at present in man because of the lack of an adequate method for the extracorporeal maintenance of the circulation, with the blood stream excluded from the heart and lungs. In the experimental animal, however, intracardiac operations may be performed under direct vision during short periods in which both venae cavae are clamped. With the expectation that eventually a practical method of oxygenating large quantities of blood outside the body will permit operation in the open human heart, experiments were undertaken to determine whether grafted tissue could be used to replace a portion of a cardiac valve.

Intracardiac operations have been performed without interrupting the circulation. The procedures have been necessarily simple ones. Sanways³⁴ in 1898 and later Brunton⁷ suggested surgical enlargement of the narrowed orifice in the treatment of mitral stenosis. Since that time many investigators, including Cushing and Branch,¹² Bernheim⁴ and Scheppelmann,³⁶ have experimentally divided valve leaflets using sharp knives thrust blindly into the heart. This method has been improved upon by Allen and Graham² who devised a cardioscope with an attached knife blade in order to see the structure being divided.

Cutler, Levine and Beck¹⁴ constructed a "cardiovalvulotome" and were the first to excise a portion of a stenotic mitral valve in human patients. Their first patient survived the operation and was apparently improved. However, in a review of all patients operated upon, Cutler and Beck¹³ in 1929 reported the deaths of their six later patients and of the single patients of Allen¹ and of Pribiam.³³ Souttar's⁴⁰ patient, whose mitral valve was dilated digitally, sur-

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† This work was supported by a grant from the Life Insurance Medical Research Fund.

vived, as did the young man whose aortic valve was dilated by Tuffier.⁴² Prior to these operations Doyen¹⁶ attempted section of the pulmonary valve in a case of congenital pulmonary stenosis with a fatal result.

Early investigators in this field were handicapped by their inability to produce in experimental animals chronic valvular lesions similar to those seen in man. This difficulty was overcome by Powers and his associates^{30, 31, 32} who produced endocarditis by repeatedly damaging the valves of dogs with the electrocautery and injecting streptococci into the bloodstream. The surviving animals developed valve lesions closely resembling those seen in rheumatic human hearts. Five dogs, with mitral stenosis produced in this manner, were operated upon. A portion of the mitral valve was removed with the cardiovalvulotome of Cutler and Beck. All died of cardiac failure within nine days of operation.

Recently Harken^{23, 24} has been successful in establishing subacute bacterial endocarditis in dogs. He has also developed an improved cardioscope. Cohn¹⁰ produced interauricular septal defects in dogs and later succeeded in closing them. Smithy and Parker³⁹ incised aortic leaflets through the wall of the aorta. None of these operators interrupted the circulation.

Other investigators have interrupted the circulation and performed intracardiac operations under direct vision. Following Sauerbruch's³⁷ description of his method of compressing the base of the heart to control hemorrhage in the surgical treatment of cardiac wounds, Haecker²² in 1907, reported a series of operations within the hearts of dogs whose venae cavae were occluded. Carrel and Tuffier^{9, 42, 43} clamped the base of the heart in some of their fascinating experiments. O'Shaughnessy²⁸ attempted to prolong the period of circulatory arrest by perfusing the heads of his animals with a solution of hemoglobin. Bjork⁵ working in Crafoord's laboratory has recently reported the successful perfusion of dogs' brains with oxygenated blood while both venae cavae were clamped. The experiments were performed under sterile conditions. Under these conditions the dogs survived, in good health, periods of occlusion as long as thirty-three minutes. Shaw and his associates³⁷ produced insufficiency and stenosis of valves on both sides of the heart in a large series of dogs whose cavae were temporarily occluded. In addition to operating with the venae cavae clamped, Fauteux¹⁷ performed some experiments in which the pulmonary artery was clamped and the left heart opened. Gibbon¹⁹ has perfused, under sterile conditions, the entire bodies of cats with oxygenated blood while the pulmonary artery was clamped. Prolonged survival in good health was reported following a period of occlusion of the pulmonary artery for 20 minutes.

Since we desired to operate within the open heart, under direct vision preliminary experiments⁴¹ were performed to determine how long dogs could tolerate simultaneous clamping of both venae cavae. Clamping up to nine minutes produced no clinical evidence of permanent neurologic damage and the mortality rate was minimal.

The work of several earlier investigators was helpful in choosing tissue

suitable for use as grafts Jeger²⁵ formed valves in vein transplants in the dog by suturing the invaginated wall of the vein in such a way that two flaps were formed One of these valves was patent and competent fourteen days after being placed in the carotid artery In 1930, Wilson¹⁵ reported placing strips of pericardium, tendon and fascia across the mitral orifice to produce stenosis The pericardial strips remained viable and did not give rise to thrombus formation Later Gordon Murray²⁷ threaded segments of vein which had been

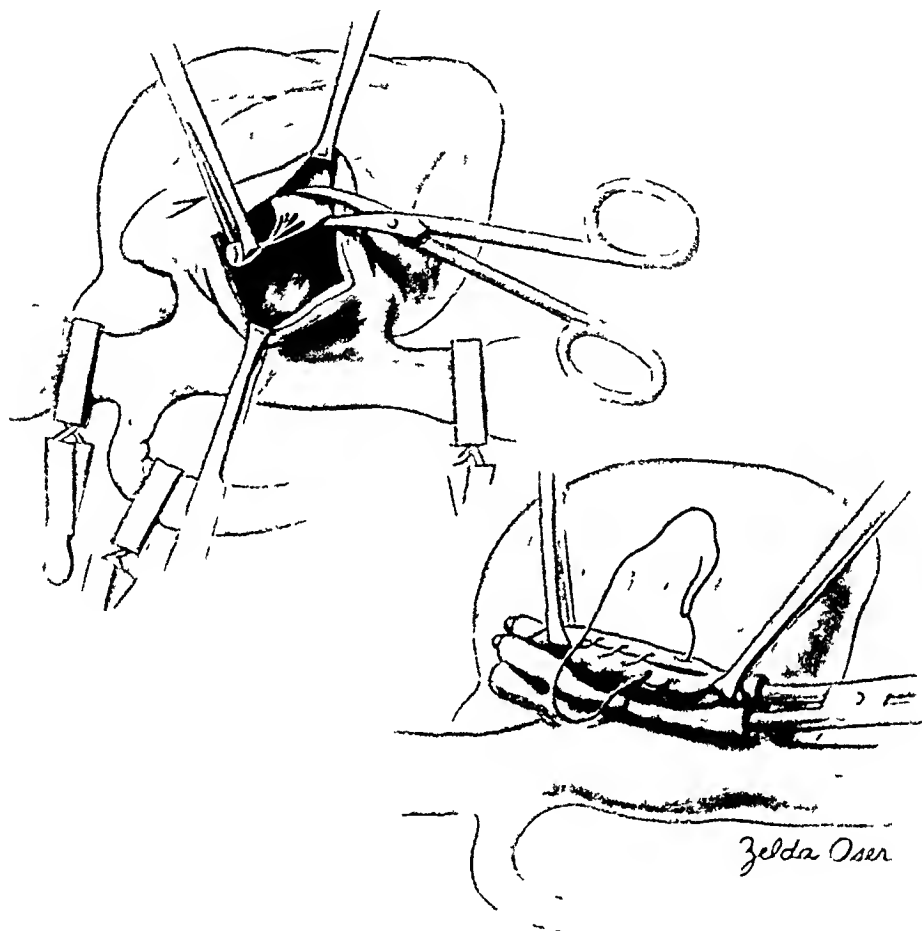


FIG 1—*Above* Resection of the valve cusp and papillary muscle
Below Temporary closure of the auricular incision

turned inside out across the left ventricle to repair defects in the mitral valve made by the cardiovalvulotome Two animals survived without evidence of cardiac decompensation These reports suggested that either vein or pericardium might be suitable as a replacement for a cardiac valve Grafts of potentially viable tissue were thought to be preferable to foreign material such as the ingenious methyl methacrylate valves placed in the aorta by Campbell⁸ The following technic was therefore developed to allow resection of a portion of the tricuspid valve and its replacement with a graft of vein or pericardium

TECHNIC

Dogs were anesthetized with nembutal 25 mg per Kg body weight intra-

venously Air was administered endotracheally under intermittent positive pressure The right pleural cavity was entered through the bed of the resected fourth rib Both venae cavae were isolated and the azygos vein was ligated and divided or temporarily clamped The pericardium was opened widely and two fine silk stay sutures placed in the wall of the right auricle

Bulldog clamps were applied to both cavae completely occluding them An incision about three centimeters long extending into the auricular process was made in the right auricle parallel to the annulus fibrosus Very little bleeding occurred Under direct vision the papillary muscle attached to the right cusp of the tricuspid valve was grasped and divided With traction on the divided papillary muscle the right cusp was drawn into the auricle and divided along its base where it is attached to the wall of the heart (Fig 1)

Saline solution was poured into the heart and the auricular incision quickly closed with a noncrushing Crafoord clamp The bulldog clamps were removed from the cavae, re-establishing the circulation The incision in the auricle was temporarily closed by a continuous suture and the Crafoord clamp removed (Fig 1)

The graft was then prepared If a vein was to be used, a generous segment of the azygos, with the supreme intercostal vein attached, was removed and pinned to a moistened cloth-covered board The adventitia was stripped away and the vein turned inside out forming a T-shaped graft covered with vascular endothelium The azygos vein formed the leaflet of the graft and the supreme intercostal vein the chorda tendinea To prevent the graft from filling with blood, the open ends of the vein were closed with fine silk Medium silk sutures were placed in the graft and tied after which they were again carried through the graft in order to approximate the graft directly to the endocardium Usually three sutures were placed at the leaflet base and one at the apex of the chorda tendinea To prevent rupture of the chorda the suture at its tip was continuous with the center suture at the base of the valve The basal sutures were threaded through half circle round pointed needles and the apical suture through a long straight needle The base of the graft was then transfixed with another long straight needle to permit it to be handled conveniently

When pericardium was used, a portion, free from fat, was resected and trimmed to the desired size and shape on the board (Fig 2, top) The suture and needle arrangement was the same as that described for the veins except that five sutures were placed at the base of the graft instead of three Sometimes grafts of other shapes were prepared Both venous and pericardial grafts with two chordae tendineae have been successfully implanted The preparation of the graft required about 45 minutes During this time the heart could recover from the effects of the first circulatory interruption

The Crafoord clamp was then replaced on the auricle and the temporary suture in the auricular wound was removed The cavae were reclamped and the Crafoord clamp removed, again exposing the interior of the right side of the heart The long straight needle attached to the suture in the chorda tendinea of the graft was passed into the base of the resected papillary muscle,

through the interventricular septum and out near the apex of the heart. This suture was tightened and the graft moved down near the auricular incision and held there on its supporting needle by the assistant (Fig 2A). The needles threaded through the sutures attached to the base of the graft were then

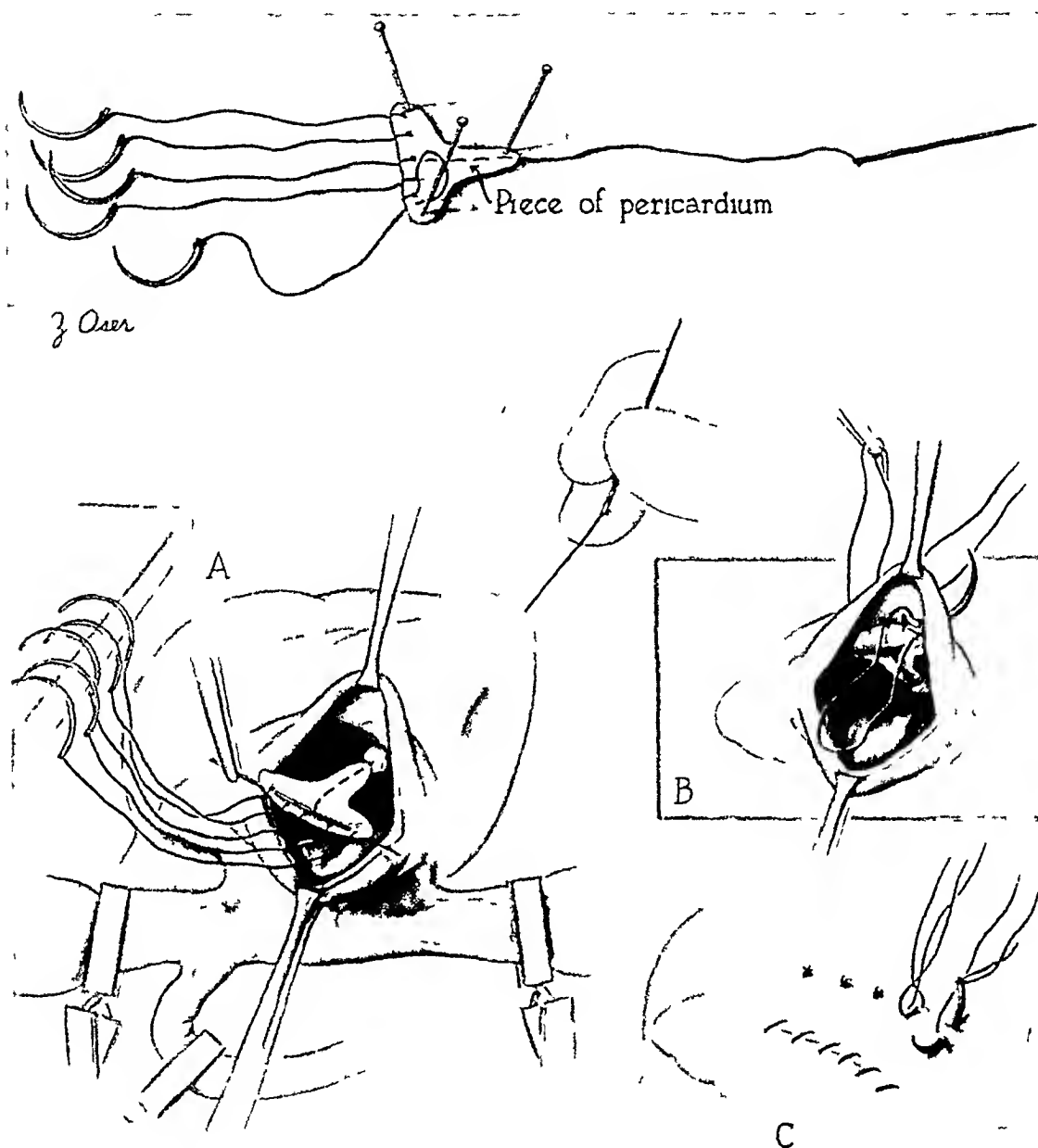


FIG 2—Above Pericardial graft with attached sutures and needles

Below (A) Apical suture placed through stump of papillary muscle, interventricular septum, and apex of heart

(B) Basal sutures placed through annulus fibrosus

(C) Auricular incision closed Basal sutures tied

passed through the annulus fibrosus from within outwards. While traction was made on all sutures the supporting needle was removed and the graft pulled into position (Fig 2B). The right heart was filled with saline containing a few minims of a 1:1,000 solution of epinephrine hydrochloride. The

Crafoord clamp was replaced closing the auricular incision and the caval clamps removed. When necessary an additional intracardiac injection of 0.3 cc of epinephrine solution was given and gentle cardiac massage instituted until strong contractions ensued. A continuous suture of fine silk was used to close the auricular incision.

The sutures holding the base of the graft were then secured by tying each one to another suture placed through the cardiac tissues at its point of exit from the wall of the heart (Fig. 2C). The apical suture was secured in similar

TABLE I

Experiment	Time of Death Days	Time of Sacrifice Days	Duration of Survival Months	Remarks
Venous Grafts				
1	0			Ventricular fibrillation
2			11	Living and well
3	9			Pericarditis
4		22		Living and well at time of sacrifice
5	0			Ventricular fibrillation
7	0			Ventricular fibrillation
8		4		Severe neurological damage
9	0			Ventricular fibrillation
10			9	Living and well
Pericardial Grafts				
11		6		Severe neurologic damage
12	32			Infection about graft sutures
14	0			Ventricular fibrillation
16	1			Ventricular fibrillation
17	28			Distemper
23	0			Ventricular fibrillation
25		3		Severe neurologic damage
26			8	Living and well
29			8	Living and well
30			7	Living and well
Control				
19		36		Living and well at time of sacrifice
20		37		Living and well at time of sacrifice
21		40		Living and well at time of sacrifice
22		39		Living and well at time of sacrifice
24			8	Living marked ascites

fashion. Care was taken to avoid injury to the coronary vessels. The pericardium was left partially open and the chest wall closed. One hundred thousand units of penicillin were placed in the pleural cavity and the same amount given intravenously. No anticoagulants were used.

The manipulations during the time the cavae were clamped were carried out as quickly as possible and every precaution was taken to avoid any technical error which might unduly prolong the time of circulatory interruption. In most of the operations adequate time was available to allow careful placing of sutures. Time required to resect a cusp of the valve averaged three minutes while suturing the graft in place took an average of six minutes.

In five control animals a leaflet of the tricuspid valve was resected as described above without replacement by a graft.

RESULTS

The operation was performed on 19 dogs with the results shown in Table I. Six animals died at operation of ventricular fibrillation. One died the first postoperative day following successful defibrillation with electric current. Two animals died of infection on the ninth and 32d days respectively. Three animals, with evidence of severe damage to the central nervous system, were sacrificed during the first week.

Seven animals were living and well three weeks after the operation. One of these was sacrificed on the 22d day and one died of distemper on the 28th day. Five dogs survived from seven to eleven months after operation. They are apparently in good condition without evidence of circulatory impairment.



FIG 3—(A) Venous graft at completion of operation (B) Resected portion of tricuspid valve

The hearts of dogs that died at operation were examined to determine whether the grafts were properly placed. The other specimens, three venous and five pericardial grafts, were obtained at autopsy from one to 32 days after operation.

At autopsy none of the animals showed any gross evidence of circulatory failure. Intrapleural adhesions were present to a moderate degree. The pericardium was always adherent to the heart at the site of the auricular suture and there were usually a few adhesions to the surface of the heart elsewhere. The lung was frequently adherent to the heart where the pericardium had been removed. The auricular wounds and the sites of excision of the valve and papillary muscle were uniformly clean and free of thrombus formation except for one specimen in which a small, firm, densely adherent thrombus was present at one end of the auricular wound.

Specimens of grafted veins were obtained on the fourth, ninth and 22d postoperative days. In every case the endothelial surface of the graft was smooth, shiny and free of clots. Two grafts were well placed and firmly adherent at all

points of suture. In the other specimen the sutures had not been pulled up snugly and the graft was suspended free in the ventricular cavity. When these grafts were placed in the heart they were flat and thin and resembled closely in appearance the normal valve cusp. At autopsy they were found to be swollen and thickened with resumption of their original rounded cross-section. Also no reinforcing suture had been placed through that part of the

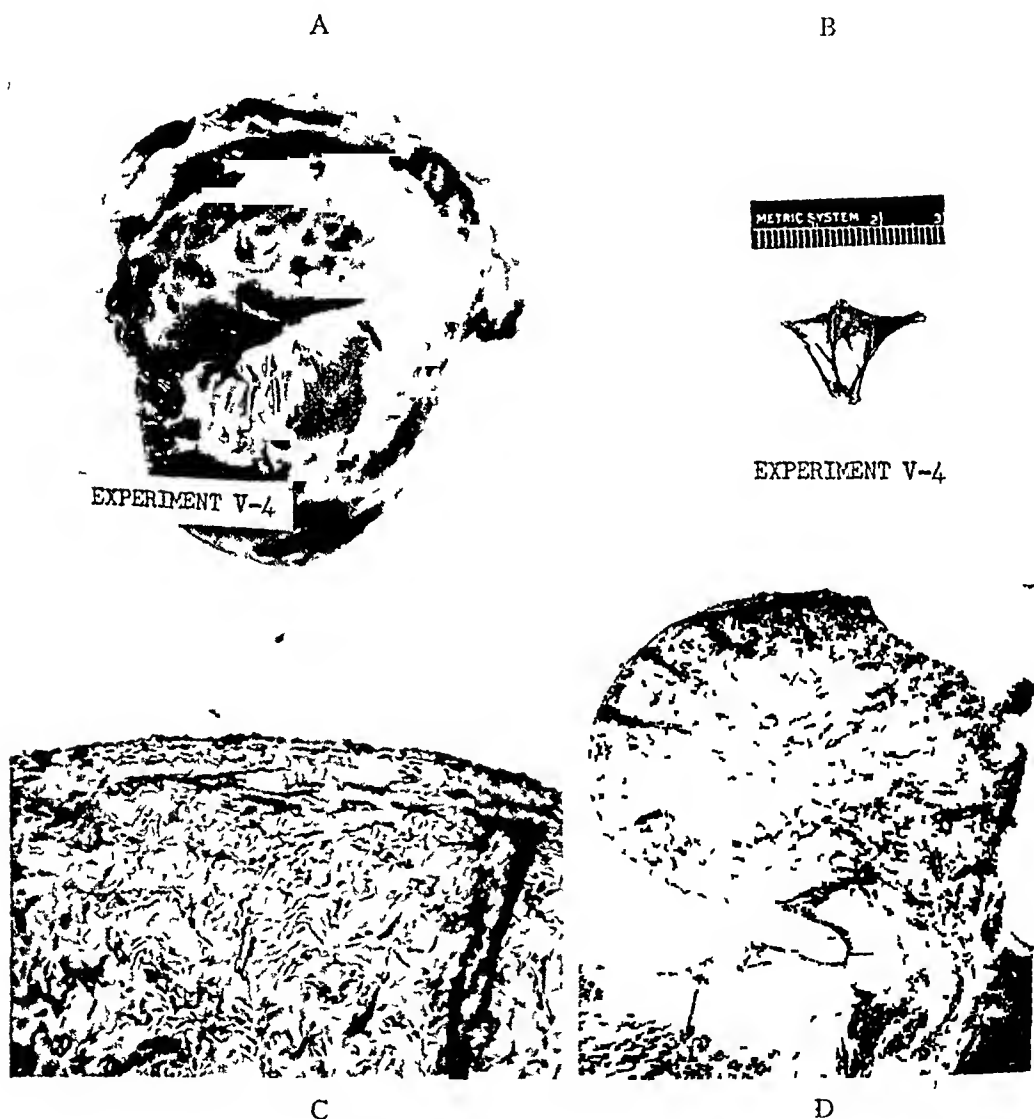


FIG 4—(A) Venous graft on twenty-second day. (B) Resected portion of tricuspid valve. (C) High power photomicrograph of surface of graft. (D) Low power photomicrograph, showing rounded cross-section of the graft with blood vessels in central portion.

graft forming the chorda tendinea in these three animals and rupture of the chorda had occurred in each case.

The microscopic sections confirmed the absence of thrombi in all three specimens. Union of the grafts to the heart wall was by firm fibrous tissue. The normal structures of the vein wall were seen in the four-day specimen.

That obtained on the ninth day, showed evidence of an acute pancarditis with many bacteria and inflammatory cells present throughout the graft itself and all layers of the heart wall. There was no evidence of necrosis or inflammation in the 22-day specimen. Its rounded cross-section was filled with fibrous tissue containing many blood vessels. The appearance of these venous grafts at the end of the operation and after 22 days is illustrated in Figures 3 and 4.

Five specimens of pericardial grafts were obtained from the first to the 32d postoperative day. These grafts were all well placed and securely attached at all points of suture. The first and sixth day specimens were covered in part by a thin layer of thrombus more pronounced at the base, and the third day graft had a large white clot densely adherent to the ventricular surface.



FIG 5—(A) Pericardial graft at completion of operation (B) Resected portion of tricuspid valve

Of particular interest was the appearance of the 28-day graft. Although several times thicker than at the time of implantation it was quite flexible and gave every indication of having been functional. Its covering blended imperceptibly with the endocardium at the points of attachment and the free edges were rounded and smooth. Microscopically there were no thrombi and the covering was similar to the adjacent endocardium. The body of the graft appeared to consist of fibrous tissue containing a few thin-walled blood vessels.

The heart of the animal that died on the 32d day showed evidence of severe localized infection with small abscess formation about each of the sutures in the graft. The graft itself was thick, nodular, and very firm and rigid. In the microscopic sections pericarditis and myocarditis were evident with areas of inflammation and necrosis surrounding the suture in the central portion of the

graft Photographs of pericardial grafts, obtained at intervals after operation, appear in Figures 5, 6 and 7

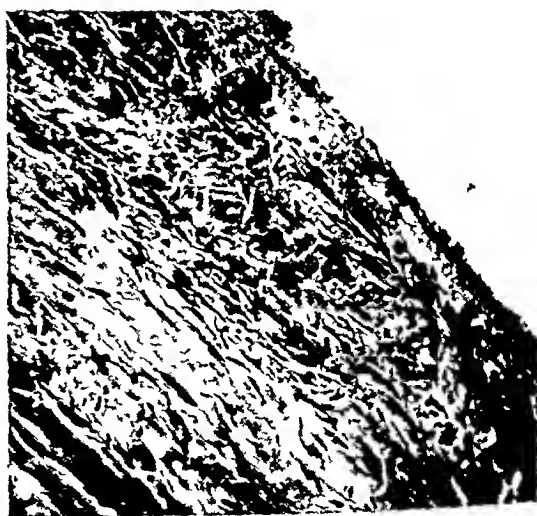
The five animals used as controls all survived the operation of tricuspid resection Four of them were sacrificed during the seventh week, at which time

A

B



EXPERIMENT V-11



C

D

FIG 6—(A) Pericardial graft on sixth day (B) Resected portion of tricuspid valve (C) Low power photomicrograph at edge of graft (D) High power photomicrograph showing thin layer of thrombus on surface of graft

they were apparently well without evidence of cardiac decompensation At autopsy it was found that from one-third to one-half of the tricuspid valve had been resected The fifth animal is still living, but marked ascites developed

approximately two months postoperatively, without other evidence of circulatory failure

An attempt to evaluate the function of the grafts was made by contrasting the clinical findings in the seven grafted animals, who survived over three weeks without evidence of infection, with the findings in the controls. In

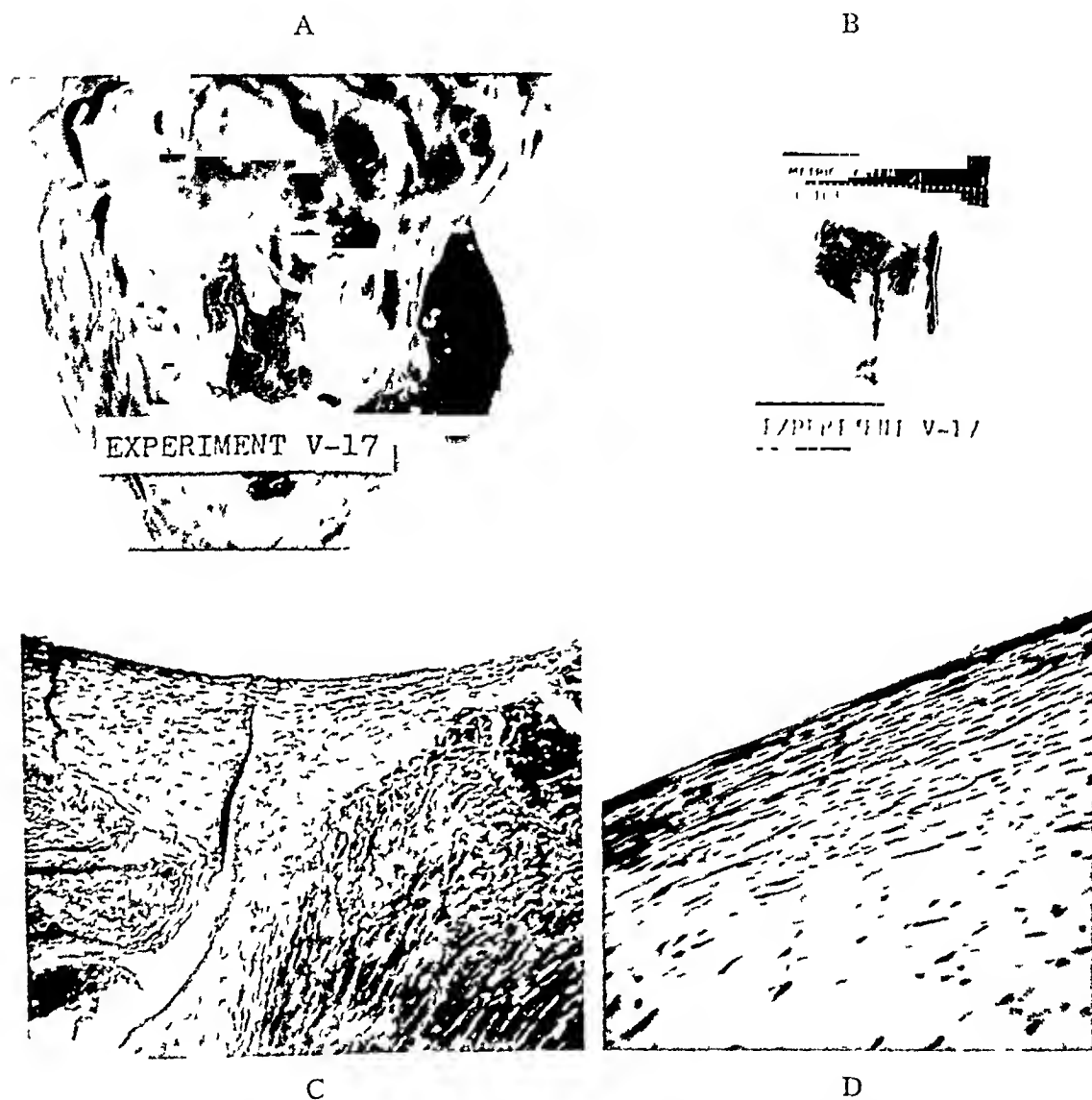


FIG. 7—(A) Pericardial graft on twenty-eighth day. (B) Resected portion of tricuspid valve. (C) Low power photomicrograph at site of attachment to heart wall. (D) High power photomicrograph showing smooth surface free of thrombus.

keeping with previous reports of tricuspid lesions in dogs, only one animal, the control dog who developed ascites, showed evidence of circulatory failure. Venous pressures were not significantly elevated in either the grafted or control animals.

The results of electrocardiographic and phonocardiographic studies, together with notes on murmurs and thrills, are shown in Table II. All the control group had prominent systolic murmurs confirmed by phonocardiogram, and marked systolic thrills. Electrocardiograms in the control group

were normal in two animals, revealed transient pericarditis in two, and early right ventricular strain in one

All three animals with venous grafts had systolic murmurs of faint to moderate intensity but no systolic thrill. The murmurs were recorded by phonocardiograms in two of these animals. Electrocardiograms in the same two animals were normal. In the third animal (Fig 4) separation of the chorda tendinea from the leaflet of the graft was found at autopsy. To prevent this occurrence the reinforcing suture was placed through the chordae of the later grafts including Experiment 10. No such suture was used in Experiment 2 whose chorda tendinea may also be torn.

Three of the four animals with pericardial grafts had no murmur at all and the fourth had a very soft systolic murmur. Phonocardiograms confirmed

TABLE II—*Animals Surviving Over Three Weeks Without Infection*

Experiment	Survival	Murmur	Thrill	Electrocardiogram	Phonocardiogram
Venous Grafts					
2	Living	Short systolic	None	Normal	Confirms murmur
4	Sacrifice 22 days	Faint systolic	None		
10	Living	Medium systolic	None	Normal	Confirms murmur
Pericardial Grafts					
17	Death 28 days Distemper	None	None		
26	Living	Soft systolic	None	Normal	Confirms murmur
29	Living	None	None	Transient pericarditis and right ventricular strain	Confirms absence of murmur
30	Living	None	None	Myocardial infarct	Confirms absence of murmur
Control					
19	Sacrifice 36 days	Loud systolic	Marked systolic	Right ventricular strain	Confirms murmur
20	Sacrifice 37 days	Moderate systolic	Marked systolic	Transient pericarditis	Confirms murmur
21	Sacrifice 40 days	Very loud systolic	Very marked systolic	Transient pericarditis	Confirms murmur
22	Sacrifice 39 days	Very loud systolic	Marked systolic	Normal	Confirms murmur
24	Living ascites	Moderate systolic	Marked systolic	Normal	Confirms murmur

these findings. In Figure 8 phonocardiograms are reproduced from a normal dog, from a typical control animal with tricuspid resection alone and from two dogs with pericardial grafts but without murmurs or thrills. There were no palpable thrills in any of the four animals. Electrocardiograms were normal in one dog, showed transient right ventricular strain and pericarditis in another and myocardial infarction in a third. This infarct could have resulted from damage to the right coronary artery by a suture, or by the electric shocks used to treat ventricular fibrillation at operation since one of the electrodes was found to be improperly padded.

DISCUSSION

The disadvantages inherent in any technic in which complete interruption of the circulation is necessary have been emphasized by other authors.^{2, 16, 17}

The large number of deaths from ventricular fibrillation in our series and the occurrence of severe neurologic damage in three animals indicate that these disadvantages have not been overcome. In spite of this it has been possible to replace the resected portion of a cardiac valve with a graft sutured under direct vision.

Morphologically the pericardial grafts appear to be better than the venous grafts. Although covered with vascular endothelium and free of thrombi the veins tended to become swollen and revert to their original round cross-section losing the valve-like shape which they had at the time of operation. The pericardial grafts, on the other hand, remained thin and flexible and appeared to

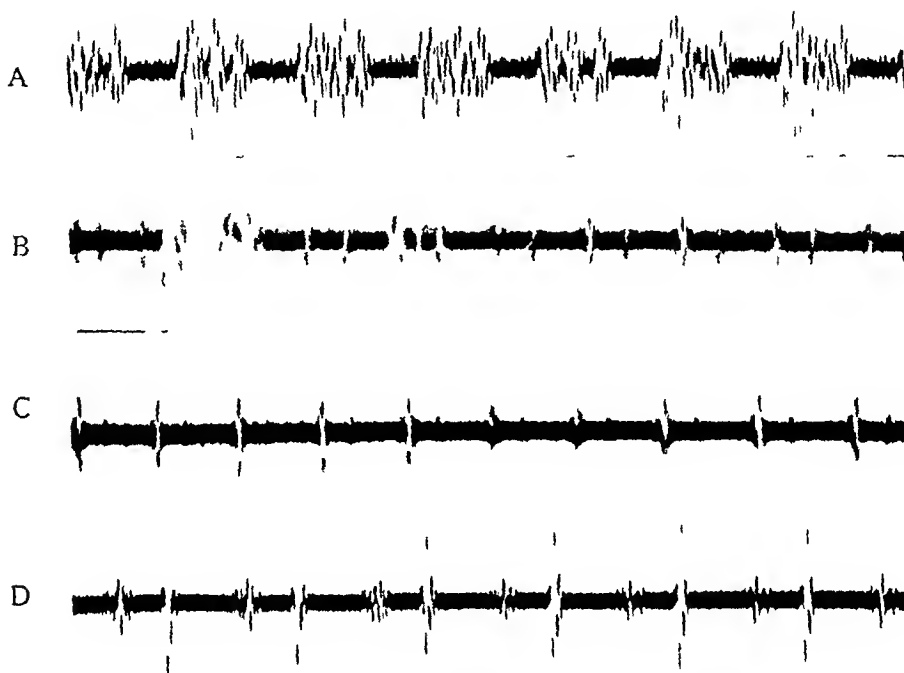


FIG 8—Phonocardiograms

- A Control dog with resection alone (Experiment 19)
- B Pericardial graft (Experiment 30) (The blurring of the graphic record in two places is due to respiratory movements)
- C Pericardial graft (Experiment 29)
- D Normal dog

meet the morphologic requirements for functional valves. The early specimens had a thin layer of thrombus formation and in one specimen a large clot was present. The late specimens were only slightly thickened and had a smooth shiny surface.

Clinically the pericardial grafts also gave better results. Three of four dogs had no murmur and thrill, one to eight months after operation. In contrast the dogs with venous grafts all had systolic murmurs and the control dogs without grafts had marked murmurs and thrill and one developed ascites.

A temporary extracorporeal circulation should greatly reduce the mortality of intracardiac operations under direct vision. Deaths from damage to the central nervous system and from ventricular fibrillation should be eliminated.

because of the adequate supply of oxygenated blood to the cerebral and coronary arteries. In addition the surgeon should be able to perform more meticulous and extensive operations, because he will not be limited to the few minutes of circulatory interruption that the brain will tolerate.

SUMMARY

1 In 19 dogs, a cusp of the tricuspid valve was replaced by a graft of vein or pericardium sutured in position under direct vision.

2 Seven of these dogs survived in apparent good health from three weeks to seven months after operation.

3 Specimens of the grafts obtained at autopsy after three weeks were viable and firmly united to the wall of the heart.

4 In five control animals a portion of the tricuspid valve was resected and no graft was used. Postoperatively these animals had loud murmurs and marked precordial thrills, in contrast to the grafted animals in which there were no thrills and faint, or no, murmurs.

5 Anatomically and functionally the pericardium appeared to be more suitable than a vein as a source for the graft.

SUPPLEMENTARY NOTE

Since submission of this article for publication, changes have occurred in the state of the surviving animals. Animals 2 and 10 (vein grafts) have developed palpable thrills, and the murmurs previously heard have increased in intensity. Dog 10 was sacrificed. The right heart was enlarged and the graft was cord-like and useless. It was attached only at one end of the base and at the apex. Animals 26, 29 and 30 (pericardial grafts) have systolic murmurs of moderate intensity, and a systolic thrill can be felt in dogs 26 and 30. Dog 26 was sacrificed. The heart was normal in size with a well-placed, intact, firmly attached graft. The surface was shiny and blended smoothly with the endocardium. The leaflet, however, was somewhat contracted upwards toward the base.

ACKNOWLEDGMENTS

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THE METABOLISM OF CALCIUM IN PATIENTS WITH SPINAL CORD INJURIES*

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FOR THE OPINIONS EXPRESSED OR CONCLUSIONS DRAWN BY THE AUTHOR

RECUMBENCY HAS BEEN RECOGNIZED as an important factor in the genesis of urinary tract calculi^{5, 11, 21} The literature concerning the factors involved in calculus formation is very extensive^{3, 17, 20, 22, 23} Considering that the major factors include recumbency, stasis, infection, and dietary dyscrasias, it is not at all surprising that patients suffering from injury to the spinal cord should have a high incidence of calculi in the urinary tract The following report is based on observations made on over 700 young male adults (ages 18-50) who had suffered injury to the spinal cord during and shortly after World War II

In the first world-wide conflict, concentration of patients with spinal cord injury at special hospitals led Head and Riddoch¹⁵ to list the course of paraplegia in four stages These were (1) The stage of flaccidity which began with the onset of the injury and continued for about six weeks, (2) The stage of spasticity when reflex activity developed and gradually increased in severity, (3) The stage of paraplegia in flexion when the spastic contractions had continued to the point where contractures had developed, and (4) The stage of loss of reflex activity which developed as debility and sepsis advanced, with death as the final culmination Undoubtedly, the history of the patients from the recent war would have been the same were it not for the advent of anti-bacterial agents and the recognition of the need for highly supervised bladder care such as that described by Munio²⁶ As a consequence of these advances, the outlook for the patient with spinal cord injury was improved Despite this, two grave problems remained—the high incidence of urinary tract calculi with the concomitant presence of severe urinary tract infection, and the debilitating effect of huge decubitus ulcers The latter problem was solved by the development of surgical techniques such as those of Gibbon & Freeman¹⁴ and others^{2, 7, 32} The former was more difficult to solve, for the treatment of the injury was recumbency, and mobilization could not be accomplished since the lower limbs (and in quadriplegias, all four limbs) were paralyzed To attempt an answer, certain data appeared to be necessary

INCIDENCE OF URINARY TRACT CALCULI

Survey of the initial group of 90 patients demonstrated that renal stones were present in 15 and bladder stones in 12 or an overall incidence

* Submitted for publication, April, 1948

of 30 per cent. Subsequent analyses of other groups of patients showed that 38.4 per cent of 164, and 27 per cent of 280 had urinary tract calculi in the first months of injury. These figures were in accord with those observed at other centers for the care of paraplegic patients.¹⁸

a *Relationship to age* The age range of these patients was from 18 to 50 years with the average age being approximately 25 years. No correlation could be observed between age and incidence of calculus formation.

b *Relationship to level of lesion* With lesions ranging from the fourth cervical dermatome down, no correlation between the level of the lesion and the incidence of stone formation could be observed.

c *Relation to dietary intake of calcium* Most of the patients were severely restricted in the amount of calcium in their diet during the early part of our experience. A few, however, insisted on liberal allotments of milk, cheese, and ice cream without any noticeable difference in the incidence of calculi.

d *Relation to urinary calcium excretion* With limited laboratory facilities available, a rough quantitation of the amount of calcium excreted in the urine by the "quantitative" Sulkowitch test⁴ was undertaken. To test the accuracy of the method, samples of urine from normal ambulant males were submitted at intervals along with the test samples, all as unknowns. Normals were found to excrete approximately 150 milligrams of calcium daily in 1500 cubic centimeters of urine by the method used. Despite the relative inaccuracies of the method, there was little question about the fact that the patients with extremely high daily excretions of calcium were "stone formers." Conversely, those with low daily outputs of calcium did not form stones. Because of this finding, a study of the factors entering into the increased excretion of calcium (and the formation of stones) was undertaken.

RECUMBENCY

Recumbency was the most obvious feature to examine first. Patients showed daily excretions of calcium in excess of 500 mg. as early as the first week after injury. Since careful fluid intake and output records were kept on most of the patients, various other correlations were found. Among these were the fact that despite extremely high daily outputs of calcium (over 500 mg.), provided the concentration were kept below 15 mg. per cent, stones rarely formed. The concentration was directly related to the fluid intake and with the advent of strict adherence to a schedule of more than 4,000 cc. of fluid intake daily, the incidence of calculus formation was noted to fall. Even with this precaution, the per cent of "stone formers" remained at about 20 per cent. Consequently, to test concomitantly the factor of fractures of major bones *per se* and the factor of recumbency, 93 cases of arm fracture and 87 cases of leg fracture were surveyed.²³ The cases with fracture of the arm were all ambulant, only the injured extremity being immobilized. No stones were found in these cases and the average urinary calcium excretions were within normal limits. In the leg fracture cases 19 per cent showed the presence of urinary tract calculi, principally in the bladder. In these cases, the level of calcium

excretion was uniformly higher than normal, ranging from 125–350 mg daily and stones were found in those with the greatest calcium excretions. This observation is in agreement with the studies of Flocks.¹¹ There appeared to be no difference between femoral fractures treated with suspended traction and those treated with casts. This point is also borne out by the observation that paraplegic patients with almost continuous reflex spastic activity of the legs were as vulnerable to the formation of stones as were those with complete flaccidity. As such, it appeared likely that the principal factor involved was not recumbency alone, nor the presence of a fracture of a major bone, but the absence of weight-bearing on the long bones of the legs. To test this hypothesis

FIGURE 1

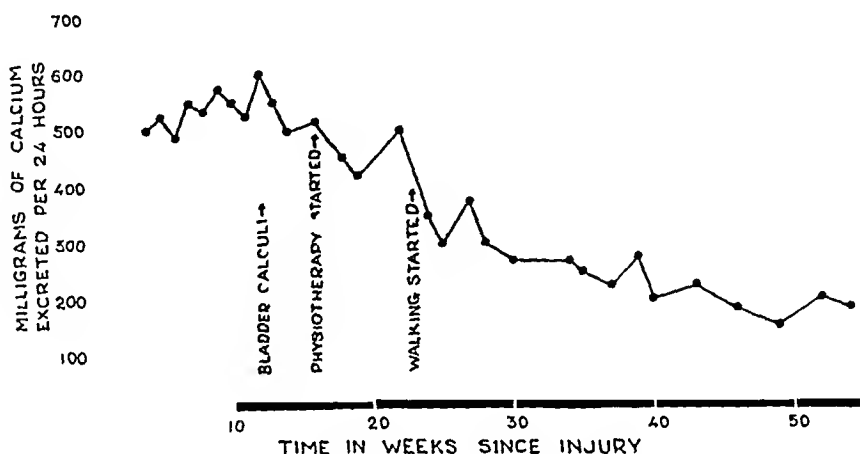


FIG 1—Patient with injury to spinal cord at D₁₂ dermatome. This patient was one of the first to ambulate and demonstrates the sharp drop in urinary calcium excretion coincident with this procedure. Later, when his right hip dislocated and ambulation had to be discontinued, stones reformed in the bladder.

paraplegic patients were first mobilized in wheel chairs, but high urinary calcium excretions were maintained despite this change. Then, they were equipped with crude metal straps as long leg braces. Following even feeble attempts at ambulation in a walker, calcium excretion fell markedly in all patients studied. The events from the time of initial observation to the conclusion of the period are represented graphically for two patients in Figures 1 and 2. These cases show the major features very strikingly and the resultant lessons learned gave impetus to the development of techniques which would allow for early and vigorous ambulation.¹¹

Blood studies failed to reveal a single instance of significant elevation of total blood calcium. No change in blood phosphorous or phosphatase was noted in a group of 12 cases. Further study is definitely needed in this sphere, for complete and well regulated studies were not carried out, due to exigencies beyond control.

The role of *Vitamin D* was investigated but in more than 25 patients, liberal doses failed to alter the excretion of calcium, and no change was noted on its withdrawal.

Vitamin A was also administered, but in these patients, the presence or absence of supplemental dosages failed to alter the course of excretion to any significant degree

Time seemed, at first, to be a major factor, for on cursory analysis of the figures, the rate of stone formation and the level of calcium excretion usually fell sharply at about the eighth month. However, subsequent analysis demonstrated that these phenomena occurred coincidentally with the institution of ambulation.

Vicarious deposition of calcium salts Certain patients showed peculiar depositions of roentgen ray opaque material in the soft tissues about the hip joints. Some of these depositions showed bone lines. It was tentatively decided

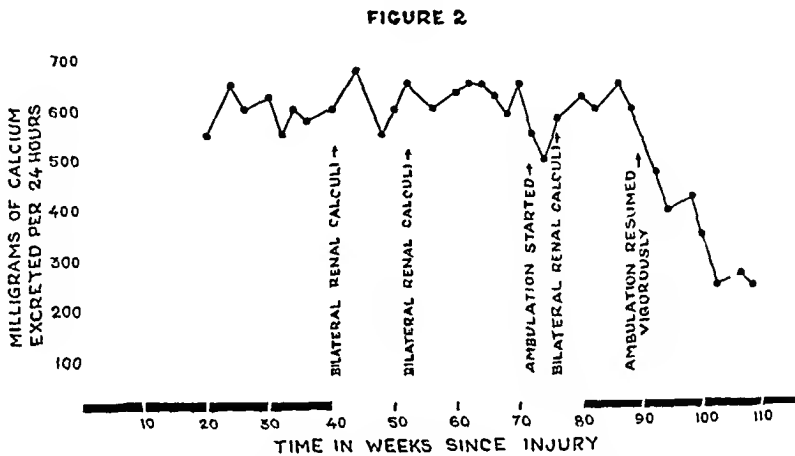


FIG 2—A patient with a spinal cord transection at D₄ dermatome. Despite the numerous examples of the benefits derived from ambulation, this patient refused to consider the difficult task of ambulation until his life was jeopardized. The resulting drop in calcium excretion is dramatically illustrated.

to label these cases as “neurogenic ossifying fibromyositis,” not because it was felt that nervous influences were important, but because the condition seemed to be peculiar to patients with paraplegia. The appearance of a report by Soule,³¹ in which it was stated that the condition appeared to be peculiar to paraplegia but was not associated with other factors, prompted a resurvey of the problem. No cases had been seen in which there was not or had not been an overlying, infected, pocketed, decubitus ulcer. We had originally postulated that the presence of bacteria had instituted changes in the relations of the calcium-phosphorus balance through the local production of enzymes (phosphatase) or local changes in acid-base balance. Several patients were found with similar changes about the knees where no ulcers had ever been. It was felt, however, that these cases merely represented the spread of infectious processes along fascial planes with concomitant local changes. Apparently, this condition is similar to that described by Dejerine *et al*¹⁰. These authors found calcification in 48.7 per cent of paraplegic patients and believed that the process was one of metaplasia.

In reference to Soule's report,¹ it must be borne in mind that the external appearance of a decubitus ulcer is always deceiving. On superficial inspection, it will not be found that the ulcers usually penetrate the subcutaneous tissues and reach wide dimensions in the deep tissues. Thus, our concern largely rested on a means of separating cases of neurogenic ossifying fibromyositis from those of frank osteomyelitis with calcific depositions. Since a number of cases were seen in which neither violent trauma nor trauma incident to physical therapy could be implicated, it was felt that other factors were responsible. Biopsy specimens from two cases grew *Staphylococcus albus* in one and *Staphylococcus aureus* in the other. From this observation, it can not be argued that infection is invariably present, but it still is remarkable that in the only two cases examined (both with healed decubiti) organisms should be cultured from the heart of the calcifications.

In many roentgenograms, calcification of the rib cartilages was seen to have progressed to an advanced degree. A review of some 30 cases from the standpoint of possible gallbladder stones failed to reveal a single instance.

DISCUSSION

The factor of recumbency has been emphasized in the discussion of important features in the formation of urinary tract calculi,^{5, 11, 21} but insufficient stress has been given to actual weight-bearing. The phases of calcium metabolism that occur during childhood with the rapid formation of new bone apparently are no longer present in the adult. As such, the counterpart must lie in the stages of recanalization of the Haversian canals that occur after weight-bearing begins, biopsy or autopsy material was insufficient to permit definite conclusions. It would appear from available data that changes coincident with weight-bearing reflect an alteration in the utilization of calcium. The analysis of Albright *et al*¹ would indicate that in the absence of usual stresses and strains of activity and weight bearing, osteoblastic activity is decreased. The decreased formation of organic matrix in the face of normal rates of resorption would produce a demineralization of the immobilized bones and a hypercalcinuria. Roentgenograms invariably show the decalcified state of the bones of the pelvic girdle and legs during recumbency with marked increase in density after the assumption of the erect, weight-bearing position. It would appear that careful studies carried out during these stages would reveal many of the important factors in bone formation. Analysis of the calculi removed from these patients at operation almost uniformly showed calcium and phosphorus as the principal constituents with carbon occurring frequently. Crystallographic examinations reveal the similarity of urinary calculi to the inorganic fraction of bone.^{12, 16} It has been demonstrated that the diffusible fraction of blood calcium, *i.e.*, the ionized calcium, increases with recumbency.⁶ Excitement, likewise increases the excretion of calcium, as do the sympathomimetic drugs.²⁷ Few are the paraplegic patients who do not show a reduced total protein with a reversal of the albumin-globulin ratio. When coupled with normal blood calcium levels this would imply an increase in the ionized calcium²⁷ and thus an increase in the

calcium available for participation in bone, or stone, formation Shorr *et al*^{9, 28, 29, 30} have conducted studies on the relationship between calcium excretion and the excretion of citric acid They point out that citrate tends to keep calcium in solution, enhanced by an alkaline medium, but diminished by the presence of bacteria which reduce the citrate content Estrogenic hormones uniformly augment the excretion of citric acid and androgens reduce it They also studied normal males confined in casts and showed an excretion of calcium double that of normal but considerably less than that shown by Howard¹⁹ in fracture patients Since gynecomastia and testicular atrophy and destruction have been observed in paraplegic patients, one can imply that, in some, there are hormonal factors which might help prevent the formation of calculi

The role of infection and of the hydrogen ion concentration of the urine were of great importance in calculus formation, for most cases studied had infection of the urinary tract, almost always with urea-splitting organisms, and thus were unfit candidates for acidification of the urine for prolonged periods of time^{8, 28} Despite clinical control of these infections, bacteriuria was still present While granting that the roles of stasis and infection in the formation of urinary tract calculi may be great, the major disorder in the paraplegic patient probably lies ahead of excretion, and the presence of calculi merely reflects the abnormally high withdrawal of calcium from the bones and its excretion in the urine

As has been pointed out by Howard,^{19, 21} once a high level of calcium excretion in the urine is obtained, not much can be done to alter the rate of excretion if the mechanisms for homeostasis remain within normal limits This would explain the failure to find abnormal blood levels of calcium and phosphorous in paraplegic patients This is emphasized by the discussion of Albright *et al*¹ These authors point out that osteoporosis is primarily a disorder of tissue metabolism and only secondarily of calcium metabolism As such, blood calcium, phosphorous, and phosphatase levels can be expected to be within normal limits The resultant hypercalcinuria could be predicted from this analysis

Much study is needed before conclusive answers are obtained In a few autopsy specimens, it was felt by one pathologist that the parathyroid glands exhibited evidences of hyperplasia Granted that this be true, whether it exists as a primary or as a compensatory phenomenon is not apparent It can only be hoped that answers to these problems will be sought and found in the vast number of paraplegic patients still in hospitals

SUMMARY

- 1 A review of clinical experiences with over 700 paraplegic patients with special reference to calcium metabolism is presented
- 2 The incidence of urinary tract calculi approximates 23-35 per cent during prolonged recumbency
- 3 Ambulation reduces the incidence of calculi to such a degree that the

presence of a calculus can be taken as an indication of the failure to ambulate sufficiently

4 Neurogenic ossifying fibromyositis is discussed as a reflection of the aberrant state of calcium metabolism in the presence of infectious and inflammatory processes

ACKNOWLEDGMENTS Thanks are due to Dr Lent C Johnson whose collaborative efforts made the calcium studies possible Without his cooperation, much delay in the institution of rehabilitative measures in the paraplegic patients under our care would have been necessary Special indebtedness to Dr Harris B Shumacker, Jr and to Dr Milton O Winternitz is also acknowledged

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DISPLACEMENT OF THE ESOPHAGUS INTO A NEW DIAPHRAGMATIC ORIFICE IN THE REPAIR OF PARA-ESOPHAGEAL AND ESOPHAGEAL HIATUS HERNIA*†

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TYPES

THE PHRASE, HIAIUS HLRNIA, unqualified, refers only to the herniation which occurs at the esophageal hiatus

There are three main types of esophageal hiatus hernia

- 1 Short esophagus with "thoracic" stomach (rare)
- 2 Normal esophagus, the stomach herniates about the esophagus into the hernial sac. However, the esophagus remains in its normal situation and does not occupy a position in the sac (para-esophageal) (Approximately 33 per cent of instances)
- 3 Normal esophagus, the stomach herniates through the esophageal hiatus pushing the esophagus ahead of it into the sac (Approximately 66 per cent of instances)

The first type probably is not a true hernia of the stomach into the hiatus, as the stomach never occupied a position in the abdomen. It represents a true congenital anomaly. The other two types are also congenital, however, only in the sense that an inguinal hernia is congenital. Even though these defects are present from birth, no symptoms are usually present until the patient is 40 years or older. Apparently, it is usually necessary to have other concomitant abnormalities present before symptoms are produced. These abnormalities are in a sense accompaniments of the aging process viz, the stretching of tissue, the loss of elastic fibers, a decrease of fat in the esophageal ring, and an increase in the intra-abdominal pressure, secondary to obesity, cough, constipation, pregnancy, and ascites¹

FREQUENCY

By no means a rare defect, it has been estimated that under the conditions of general medical practice, symptoms sufficient to bring the patient to the roentgenologist for a gastro-intestinal study will result in the discovery of an esophageal hiatus hernia in two out of every 100 patients examined.²

Harrington³ operating upon 500 patients for other reasons, found that in 65 per cent, the diaphragmatic relations were normal, in the remaining 35 per cent, one or more fingers could be inserted between the esophagus and the diaphragm. This peculiarity exists more often after the fourth decade and

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occurs more frequently in females Ude and Rigler¹¹ noted that females outnumbered males 15:4. The majority of patients were advanced in age, revealing histories of multiple pregnancies, some with intra-abdominal tumors and ascites. Rigler and Eneboe⁸ attempted to evaluate the effect of increased intra-abdominal pressure in the development of hiatus hernia. They subjected women in the third trimester of pregnancy to roentgen-ray examination of the stomach. They concluded that small hernias through the esophageal hiatus were found in 18.1 per cent of multiparas and in 12.8 per cent of all cases. In seven positive cases, the hernia was not demonstrable after parturition.

RECOGNITION

In general, the symptomatology depends upon the mechanical interference to the function of the herniated organs *per se* or by the pressure on those organs encroached upon within the thoracic cage. Obviously a wide range of variables are present from patient to patient and within the same patient at different times. Therefore, it is possible to have symptoms referable to the gastro-intestinal tract, the cardiovascular system, the respiratory tract, or any combination of these systems.¹³

Physical examination contributes little to the diagnosis. Most patients are past 40 years of age and obese. "Inspiratory borborygmi"⁷ are unusual except in very large hiatus hernias.

Roentgen-ray examination is the most important single diagnostic aid available. The patient must be examined in many different positions and particularly in the recumbent and prone positions. In the upright position many hiatus hernias will reduce themselves spontaneously. If one suspects an esophageal hiatus hernia, this suspicion should be conveyed to the roentgenologist. Otherwise a routine upper gastro-intestinal series will be done and the diagnosis may be missed. Once the diagnosis of hiatus hernia is established, it is difficult at times to determine the presence or absence of additional pathology at the lower end of the esophagus.

There are two important occurrences one must bear in mind in this condition:

1. There is often no correlation between the size of the hernia and the severity of the symptoms although as a general rule small hernias do not produce symptoms.
2. The hiatus hernia may be an incidental finding. Therefore, one should rule out by all means available, the presence of any other lesion which may be responsible for the patient's symptoms.

TREATMENT

Once the diagnosis of esophageal hiatus hernia is established, and other causes for the patient's symptoms have been excluded, two modes of therapy are available, viz., conservative or operative.

Medical conservative management should be attempted in practically all cases. The most important single item with regard to good medical management consists of reducing the patient's weight. Many patients without fixation

of the stomach to the hernial ring (as evidenced by the reduction of the herniated viscus under fluoroscopy when the upright position is assumed) will be helped materially by the reduction of weight alone. Adjuvant measures include a bland diet taken as frequent small feedings, antacids, antispasmodics, sedatives, and the correction of constipation and flatulence. These patients should be advised to maintain an upright or semi-upright position after eating and also to avoid exercise after meals. Most patients will be benefited by sleeping with the thorax higher than the abdomen. For acute symptoms, nitroglycerin taken before meals and on retiring is of value. Surgical repair is justified after medical measures fail to give relief. Certain cases, because of the presence of adhesions or associated abnormalities, e.g., volvulus of the stomach, or the possibility of a more serious lesion of the distal end of the esophagus, are surgical problems at the outset and should be explored without any unusual delay.

In the past, the reconstruction of the esophageal hiatus has consisted of the displacement of the esophagus posteriorly against the vertebral column with application of the tissue about the diaphragmatic defect anteriorly and laterally utilizing various types of suture material. The scarcity of tissue of sufficiently good quality posteriorly to close the defect satisfactorily constitutes the disadvantage of this type of repair. Consequently, a space posteriorly results, which remains open to receive once again a subsequent herniation of the stomach into the thorax. In addition, the replacement of the esophagus into the same site it previously occupied, obliges one to attempt the repair with tissue, which previously was unable to withstand the existing stresses and strains arising in the relationship of the diaphragm and the adjacent abdominal viscera. The possibility of a recurrence in this area following the conventional type of repair appears to be a real one and might well explain many of the failures and recurrences reported in the literature.

The following material concerns itself with the presentation of 13 cases of esophageal hiatus hernia (exclusive of those cases associated with a congenitally short esophagus) treated surgically. A variation of the conventional repair was suggested by one of us, (O. H. W.)¹² and such a closure was first performed on October 25, 1944, since that time it has been employed in all cases. This repair entails essentially the displacement of the esophagus anteriorly and to the left, the closure of the diaphragm posteriorly, and the suturing of the stomach immediately distal to the esophago-gastric junction to the edge of the diaphragm with fine silk sutures. This method of repair fulfills all the requisites for a satisfactory hernioplasty, viz., displacement of the conduit (in this instance the esophagus) away from the weakened structures, utilization of healthy tissue in an anatomic reconstruction of the area, and the use of a non-absorbable suture.

Singleton (1942),¹⁰ in discussing a paper by Harrington, stated that he had repaired two esophageal hiatus hernias by anterior displacement of the esophagus. It may well be that others have done the same. Since that time no formal presentation has appeared in the literature to our knowledge.

PREOPERATIVE CARE

The conventional standard preoperative care is carried out, including the passing of a duodenal tube into the stomach prior to surgery. Continuous suction is applied to the inlying duodenal tube before any attempt is made to induce the anesthesia. Suction is employed during the operative procedure and is continued throughout this period. Anesthesia has consisted of either cycloprane and curare or a pentothal and curare mixture². An intratracheal tube with an inflatable cuff has been used in all cases regardless of whether the operative approach has been thoracic or abdominal.

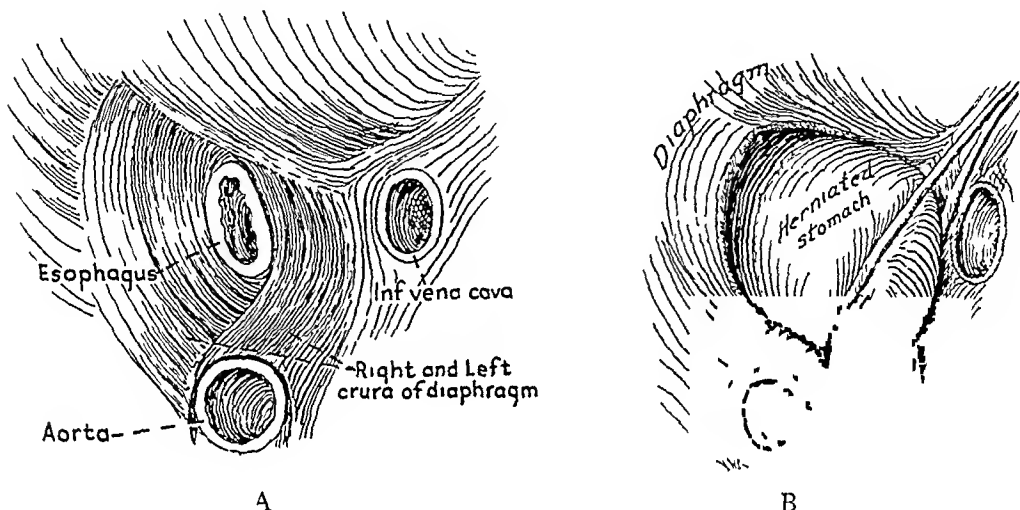


FIG 1—(A) This sketch represents the normal anatomy of the esophageal hiatus as it appears looking down upon the diaphragm from above.
(B)—The usual picture of an esophageal hiatus hernia after mobilization.

TECHNIC OF REPAIR

Transsthoracic Approach The position of the patient is a semi-lateral one with the left side elevated, the patient's back making approximately a 45 degree angle with the table. An oblique incision is made over the 9th intercostal space. In the initial operations, a segment of the 9th rib was resected. This procedure has been found to be unnecessary and has been abandoned in subsequent cases. The 9th intercostal space is incised and the pleural cavity is entered. The phrenic nerve then is crushed at its entrance into the diaphragm. The hernia is readily discernible in the triangle formed by the left ventricle, the aorta, and the diaphragm. The sac is incised and partially excised, and the edge of the hernial ring is freshened. The stomach and the esophagus are mobilized and displaced antero-laterally into the most anterior portion of the hernial defect. The right and left crura of the diaphragm then are sutured together behind the esophagus with 000 silk sutures. If the consistency and the quality of the tissue posteriorly are unsatisfactory for suture or a satisfactory approximation of the diaphragmatic crura behind the esophagus is not made readily, extending the incision into the anterior portion of the left leaf of the diaphragm facilitates this part of the procedure. Moreover, this maneuver is in accord with the best principles of hernioplasty, viz., moving the esophagus to an area where a snug anatomic closure of strong tissues can be made.

DISPLACEMENT OF ESOPHAGUS

about it. Additional sutures of 0000 silk are taken from the free edge of the diaphragm to the esophago-gastric junction, preferably on the stomach side (See Fig 1 & 2 & 3). The chest closure is effected by three pericostal sutures of double strands of 0 chromic catgut, care being observed that the elements of the intercostal bundle are not caught in the suture. The remainder of the chest wall closure is accomplished by interrupted fine silk sutures in multiple layers.

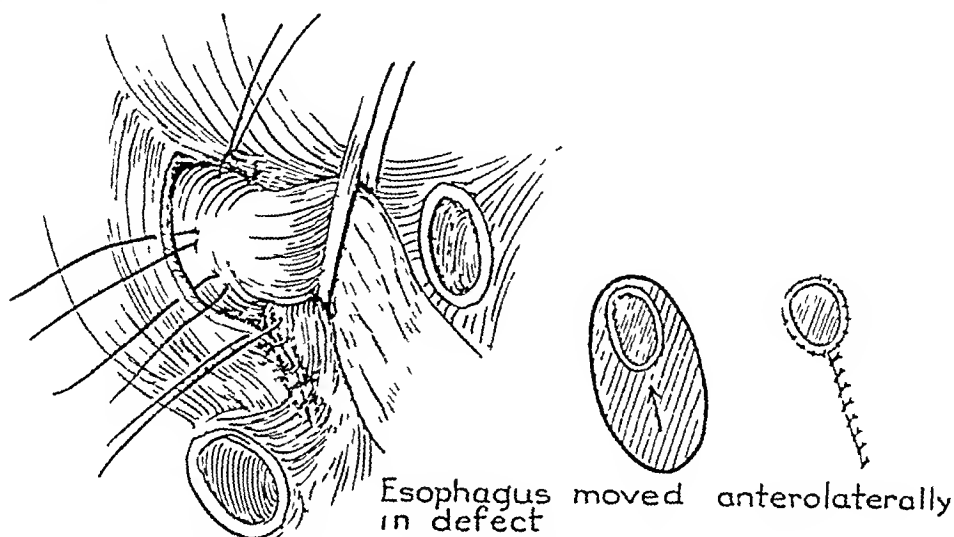


FIG 2—The herniated portion of the stomach has been replaced into the abdomen. The esophagus has been displaced anteriorly and laterally into the original defect and a closure has been effected posteriorly by suture of the right and left crura of the diaphragm. Additional sutures have been taken from the upper portion of the stomach immediately distal to the esophago-gastric junction to the edges of the diaphragm.

The inset drawings illustrate the repair diagrammatically.

This type of repair is indicated when the tissues posteriorly are of sufficiently good quality for satisfactory suture.

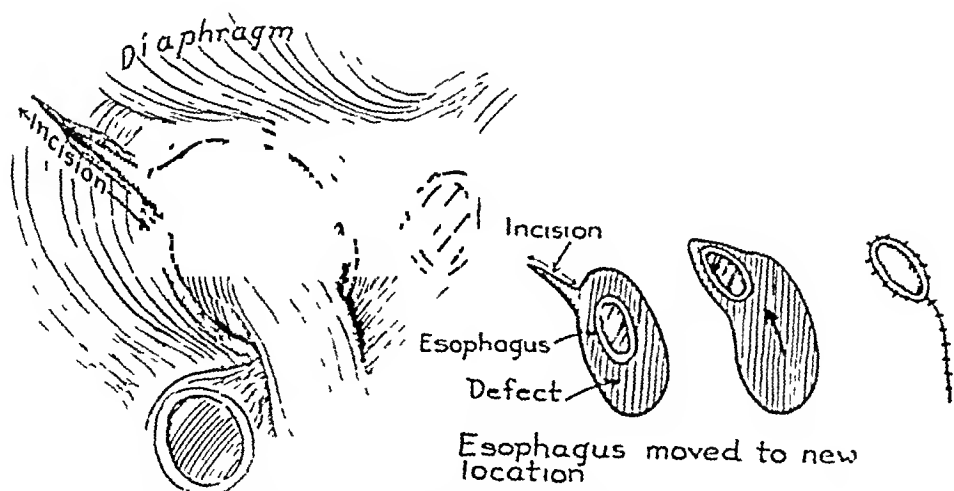


FIG 3—When the tissues of the right and left crura are not satisfactory for suture, a new esophageal hiatus is created.

The principles of repair are identical in all respects to those indicated under Figure 2.

In both drawings the closure of the diaphragm posterior has been shown to be complete. This is not always possible from the thoracic approach. However two or three well-placed sutures posteriorly approximating the diaphragm suffices to insure a good result.

Abdominal Approach The patient is operated upon in the supine position. A subcostal incision is employed. All bleeding is controlled with fine catgut and silk. The gastro-colic ligament is identified, and an appropriate sized opening is made into the lesser omental sac. With traction upon the stomach downward and medially combined with manipulation about the hernial site reduction can usually be accomplished. At times the severance of adhesions will be necessary. The hernial ring is freshened, the sac is not excised. The stomach and esophagus are displaced anteriorly and the right and left crura of the diaphragm are sutured together with 000 silk. Usually it is possible to close the posterior defect completely from the abdominal approach. Additional sutures are taken about the periphery of the hernial ring to the uppermost portion of the stomach, with attention to the avoidance of inclusion of the vagus nerves in the suture. The abdominal closure is completed by multiple layers of 000 and 0000 silk.

Combined Abdomino-thoracic or Thoraco-abdominal Approach The patient is placed supine on the table with the left side moderately elevated. The left arm is elevated and/or placed across the chest. The incision begins at the right lateral border of the right rectus abdominus muscle, and is continued obliquely upward crossing the mid-line half-way between the xiphoid process and the umbilicus. Abdominal exploration then may be done. If abdominal pathology is present, the incision can be extended towards either side of the abdomen. In the absence of abdominal pathology or if there is need for a combined abdomino-thoracic exposure, the incision may be continued into the 9th intercostal space on the left side. This necessitates the section of a single cartilage.

The repair of the esophageal hiatus or para-esophageal hernia is effected in the same manner as previously described for the transthoracic approach by anterior displacement of the esophagus and closure behind of the right and left crura of the diaphragm.

Others^{3, 4, 6} have advocated this combined approach for lesions of the lower end of esophagus, the upper end of the stomach, and for diseases of the spleen.

Obviously if the original incision is transthoracic, if necessary the incision may be converted into a combined thoraco-abdominal approach in the presence of a lesion in the lower esophagus or upper stomach.

POSTOPERATIVE CARE

Postoperative suction is applied to the intubing duodenal tube for 24 to 48 hours. During this period appropriate amounts of sodium chloride and glucose solution are administered intravenously. When the patient tolerates well the clamping of the nasal tube, it is removed. A gradual increase in the diet is allowed. All patients have been ambulatory within the first few postoperative days. If an undue amount of fluid accumulates in the pleural cavity aspirations occasionally may be necessary.



B

FIG 4—Case No 2 U H No 749170 These x-rays represent two independent upper gastro-intestinal series taken postoperatively. The phenomena present may represent vagus nerve injury (A)—(11/22/44) The stomach is filled with food and fluid although the patient had not had either for at least 15 hours. Peristalsis appears to be very slow but moderately active. Emptying takes place very slowly. Amyl nitrite was inhaled and the patient obtained a marked physiologic response but with little effect on the emptying of the stomach. (B)—(5/21/45) After an interval of six months, another gastro-intestinal series revealed a markedly dilated proximal end of the stomach with a considerable accumulation of food and fluid. An extraordinary type of hour-glass constriction was shown in the middle third of the stomach, but the remaining portion of the stomach from that point on was rather sinuous and narrow. About seven and one-half hours after the barium was given a small amount passed through the pylorus into the first portion of the duodenum. Emptying time was extremely slow. Larocaine instilled through a stomach tube had no effect upon the configuration of the stomach.

RESULTS AND DISCUSSION

Thirteen cases of hiatus and para-esophageal hernias of the diaphragm have been repaired by the technic described herein. Nine cases were approached through the thorax, three through the abdomen, and one by the trans-abdomino-thoracic route (See Table I). No recurrences have been observed in this small group of cases in followup periods varying from five to 36 months. The two methods of repair used have proven to be simple and efficacious, the avoidance of the vagus nerve being the only consideration necessary other than the actual repair itself. This danger is inherent in any repair of an esophageal hiatus hernia (Case 2, Table I) probably represents an example of injury to the vagus nerves (See Figure 4).

The repair may be accomplished with facility through the chest or abdomen. Because of the ease of access to and exposure of the hiatus area, and the simplicity of obtaining a secure anatomic repair the transthoracic approach is to be preferred. In those cases in which the crura of the diaphragm posteriorly are not satisfactory for closure behind the displaced esophagus, we have found it advantageous to make an incision into the normal anterior margin of the left leaf of the diaphragm in order to have available healthy normal tissue for a solid closure posteriorly. This maneuver can only be accomplished safely through the thorax. In this fashion an entirely new site is created for the esophageal bed. One must be careful to avoid the possibility of too snug a closure about the esophagus itself. The presence of the inlying duodenal tube helps the surgeon decide this matter.

Certain disadvantages of this approach have become apparent as experience has accumulated. In one instance (Case 2, Table I) a carcinoma of the transverse colon was overlooked. Undoubtedly this lesion was present at the time of the initial operation for the diaphragmatic repair. Although one is able to do a moderately satisfactory abdominal exploration transdiaphragmatically through a thoracic incision, in the event of the presence of intra-abdominal pathology the efforts of the surgeon will be gravely hampered by this approach. The disadvantages to the operator may be modified somewhat by the conversion of the thoracic incision into a combined thoraco-abdominal one by the section of the costal cartilage and the anterior abdominal wall.

After any intrathoracic operation, a serous effusion follows. This transudate represents a normal protective response of the pleura to trauma. The effusion is usually small and of no consequence. However, when hemostasis has been incomplete, a bloody effusion results. The dangers of a chronic hemothorax have been well documented (Case 6, Table I) is an example of such a complication. A multiloculated empyema cavity resulted, which necessitated surgical drainage and a rather prolonged convalescence. Although the empyema healed completely on drainage alone, it might have been wiser to have performed a decortication of the lung early in the convalescent period. As has been related earlier, however, most effusions are of a minor nature. Although the potential danger of secondary infection is ever present, the use of antibiotics has in a large measure obviated this danger. In view of the fact

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TABLE I—*Transthoracic Approach*

Symptoms		Preop Diagnosis	Operation	Complications	Result
1	F S UH No 749117 46 year old white male Date of operation 10/25/44 Discharge 11/3/44	Severe	Para-esophageal hernia	Esophagus displaced antero- laterally with suture of the right and left crura behind	None Norecurrence of hernia Symptom free
2	A L UH No 749174 59 year old white female Date of operation 11/1/44 Discharge 11/8/44	Mild of short duration Some vomiting	Massive hiatus hernia, par- tial volvulus of the stomach	Incision into the diaphragm with suture behind	Massive dilatation right with effusion and gastric retention Readmitted 5/3 45 with carcinoma of trans- verse colon with radical re- section Expired 6/7/45 Gastric retention still pres- ent
3	F M UH No 750827 18 year old white male Date of operation 1/31/45 Discharge 2/7/45	Mild to moderate nausea and vomiting periodically since childhood	Massive diaphragmatic her- nia with a portion of the stomach in the right chest	Esophagus displaced antero- only with suture of right and left crura behind	None Norecurrence of hernia Symptom free
4	L O UH No 755718 64 year old white female Date of operation 7/17/45 Discharge 7/28/45	Dysphagia with severe symp- toms	Large hiatus hernia, ? car- cinoma of lower esophagus	Esophagus displaced antero- laterally with suture of crura behind	None Norecurrence of hernia Symptom free
5	E W UH No 710007 55 year old colored female Date of operation 7/19/45 Discharge 7/28/45	Moderately severe	Recurrent hiatus hernia, previous abdominal repair of the conventional type	Esophagus displaced antero- laterally with suture of crura behind	None Norecurrence of hernia Symptom free
6	N O UH No 757889 37 year old white male Date of operation 9/21/45 Discharge 9/26/45	Severe	Hiatus hernia	Esophagus displaced antero- laterally with suture of crura behind	Readmitted 10/1/45 with multiloculated empyema left, drained in multiple sites Norecurrence of hernia Symptom free Patient has residual symptoms related to his obliter- ated pleural cavity
7	E E UH No 764597 64 year old white female Date of operation 4/12/46 Discharge 4/20/46	Severe dysphagia	Hiatus hernia	Esophagus displaced antero- laterally with suture of crura behind	Some dysphagia to solid foods for a temporary pe- riod Norecurrence of hernia Symptom free

TABLE I (Cont'd)—*Transthoracic Approach*

Symptoms		Preop Diagnosis	Operation	Complications	Result
8	I P Ull No 761516 61 year old white female Date of operation 5/10/46 Discharge 5/14/46	Dysphagia, severe	Para esophageal hernia ? Esophageal stricture, ? carcinoma	Esophagus displaced antero laterally with suture of crura behind	None Norecurrence of hernia Symptom free
9	I M Ull No 766153 69 year old white male Date of operation 7/16/46 Discharge 7/27/46	Severe, vomiting hematemesis	Massive hiatus hernia Vo- lulus of the stomach	Incision into diaphragm with suture behind	Some gastric retention with pyloric obstruction Re- explored transabdominally 7/28/46 The adhesions creating torsion were severed
10	E W Ull No 616650 60 year old white female Date of operation 3/26/46 Discharge 4/1/46	Moderately severe, refer- able to para esophageal her- nia and/or gall bladder	Para esophageal hernia ? cholecystitis	Esophagus displaced antero- laterally with suture of right and left crura behind, chole- cystectomy	None Norecurrence of hernia Symptom free
11	T K Ull No 766421 59 year old white female Date of operation 8/1/46 Discharge 8/7/46	Weakness weight loss, se- vere anemia secondary to GI bleeding ? of ulcer in stomach at constricted area of esophagus Arthritis	Para esophageal hernia se- vere secondary anemia	Esophagus displaced antero laterally with suture of right and left crura behind Sub- total gastrectomy Appen- dectomy	None Norecurrence of hernia Gain in weight etc
12	I M Ull No 773601 59 year old white female Date of operation 1/14/47 Discharge 1/19/47	Moderately severe Three previous bouts of hemate- mesis and melena	Moderate sized paraesophageal hernia ? ulcer in herniated stomach	Esophagus displaced antero laterally with suture of right and left crura behind Splen- ectomy Appendectomy	None except for slight wound infection Norecurrence of hernia Symptom free
13	W T Ull No 777831 61 year old white male Date of operation 5/12/47 Discharge 5/23/47	Moderate with slight acid eructations Frequent small feedings with sensation of fullness	<i>Abdomino Thoracic Approach</i> Para esophageal hernia	Displacement of esophagus anteriorly with sutures of right and left crura behind	Pleuritic reaction in right chest with friction rib P O urinary retention due to prostate enlargement No recurrence Symp- tom free

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that the cases presented represent the efforts of several surgeons, it is surprising that a large number of patients escaped additional complications

One patient (Case 3, Table I, Figure 5) was explored through the right thorax. The differential diagnosis between a pleuro-peritoneal hiatus hernia and esophageal hiatus hernia could not be made preoperatively. Although a satisfactory repair was obtained, in retrospect, the left thoracic approach would have allowed the operative procedure to have been performed with greater ease.



FIG 5—Case No 3 U H No 750827, A—(1/19/45) Preoperative films

B—(3/13/45) Postoperative films, the stomach is in its normal position, the stomach empties well

This patient was a problem in diagnosis as well as therapy. He was explored through the right thorax because the possibility of a pleuro-peritoneal hernia was considered strongly. The repair as previously described (See text) was carried out with great difficulty because of the interposition of the inferior vena cava and the necessity of working around a "corner." In retrospect, if the diagnosis of esophageal hiatus hernia could have been definitely established preoperatively, the operative repair would have been facilitated by a left transthoracic approach.

The combined abdomino-thoracic approach undoubtedly allows the operator a perfect exposure of the involved area as well as the best opportunity for a satisfactory anatomical repair. However, the disadvantage of this incision relates itself to the complicated and time consuming closure of the operative wound as well as the possibility of a chondritis should a wound infection ensue.

If in addition to the hiatus hernia, there are known abdominal lesions present the trans-abdominal or a combined abdomino-thoracic approach is to be preferred. The type of repair described herein can be accomplished satisfactorily as exemplified by the four cases approached in this manner.

In the event that one is unable to ascribe all the symptoms present to the hiatus hernia, one should deal surgically at the same sitting with the other intra-abdominal organs involved in a disease process. Anemia is not an infrequent accompaniment of hiatus hernia. Cases with anemia in the presence of occult blood in the stools without a lesion demonstrable by roentgen-ray study,

have been explored trans-thoracically. In our experience, following hernioplasty, the occult blood in the stool has disappeared and the anemia has been corrected in a short period of time. This suggests that these findings are an accompaniment of the disturbed anatomic position of the stomach.

The transabdominal approach avoids certain of the hazards of the thoracic approach. Certainly unanticipated abdominal findings can be dealt with more adequately through the abdomen. One must constantly be aware of the circumstance that the hiatus hernia may prove to be a mere incident to a more serious pathologic state.

Whereas the pleura reacts to trauma with a serous effusion which when infected may result in a total empyema, the abdomen responds to injury with a plastic exudate. Therefore, the dangers of a secondary infection in the abdomen cannot be compared to those which exist when such a complication occurs in the chest. Each case must be individualized and the approach to be made should depend upon the evaluation of the different factors present. Where the approach is optional, undoubtedly the transthoracic approach offers the operator the most satisfactory exposure and the best opportunity to perform a good anatomic repair.

SUMMARY

Certain aspects of the incidence, symptomatology, and the diagnosis of esophageal hiatus hernia have been discussed briefly.

A variation of the conventional method of repair of hiatus hernia of the diaphragm has been described. This method of repair now is used in this clinic to the exclusion of all others. This hernioplasty can be effected with ease either trans-thoracically or trans-abdominally, or by a combined approach. Thirteen cases (9 transthoracic, 3 transabdominal, 1 trans-abdomino-thoracic) have been presented in which this type of repair was used. No recurrence has been observed. Certain advantages and disadvantages of the various approaches have been reviewed.

The transthoracic approach is to be preferred. However, in cases in which a co-existent surgical disease is present in the abdomen, one should utilize the abdominal or combined approach.

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SIGMOIDOCUTANEOUS FISTULAE RESULTING FROM DIVERTICULITIS OF THE SIGMOID COLON*†

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SOME OF THE MOST DIFFICULT surgical problems encountered within the abdomen are those resulting from diverticulitis of the colon. Diverticulitis is among the commonest causes of sigmoidocutaneous fistulae, which frequently are very distressing to the patient and surgeon. It can be expected that the frequency of this complication of diverticulitis will be less in the future than it has been in the past, because recent therapeutic advances render operations on the colon less hazardous. The present study consisted of a clinical and pathologic investigation of a number of cases of diverticulitis of the sigmoid colon complicated by the occurrence of sigmoidocutaneous fistulae.

HISTORICAL BACKGROUND

Though an external fistula is not a rare complication of sigmoidal diverticulitis, not a great deal has been written about this type of lesion. Since the bladder and sigmoid are so closely approximated, it seems logical that fistulae of the bladder would outnumber the external variety. Johnson stated in 1944 that of all fistulae occurring in association with diverticulitis, those of the bladder were the most common.

Mayo, Wilson and Giffin in 1907, in one of the earliest reports on diverticulitis in which they presented a study of five proved and four probable cases of diverticulitis, had two patients in the probable group who had external fecal fistulae. In both patients the fistulae followed surgical operations. One of the patients had a sigmoidovesical fistula also. Mayo in 1918 noted that the abdominal wall was very rarely perforated as a result of an infectious process. Such a condition, however, accounted for a small percentage of the cases in which fistulae occurred in the lower part of the abdomen secondary to diverticulitis. Many of these fistulae healed spontaneously with the passing of time, he found. Sutton in 1921 stated that one encounters sigmoidovesical fistulae more frequently than those between the sigmoid and small bowel or sigmoid and skin. David in 1929 reported two cases of sigmoidovesical fistula in which external fistulae also developed after surgical drainage of abscesses. Rankin and Gorder

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studied 264 consecutive fecal fistulae at the Mayo Clinic and found 22, or 8.3 per cent, to be due to diverticulitis. Lewis and Penick in 1933 discussed 129 fecal fistulae seen at the Johns Hopkins Hospital from 1892 to 1931, only one of which was the result of diverticulitis, this fistula followed surgical drainage of an abscess, and it closed spontaneously within a short time. Jones^{7, 8} in 1936 and 1938 advocated that resection be done after the acute inflammatory process had subsided. Fistulectomy usually was contraindicated, in his opinion. In 1939, Dixon noted that when drainage of an abscess in perforative diverticulitis was necessary, a fistula frequently resulted. Some of these healed spontaneously. If such did not occur, colostomy was done proximal to the diseased segment of bowel. If the fistula persisted, closure of the fistula or segmental resection of the bowel was indicated, depending on the extent of the diverticulitis. Ginzburg in 1940 found that two of 62 external fecal fistulae studied by him were caused by diverticulitis.

Schlicke and Dixon in 1940 classified acquired external fecal fistulae according to their etiology as pathologic, traumatic and postoperative. According to them, diverticulitis and carcinoma were the common causes in the pathologic group. Since fistulae due to diverticulitis tend to heal spontaneously and since surgical operation to effect closure in such cases carries a mortality rate estimated at between 8.9 and 49 per cent, they advised that conservative therapeutic measures be given a fair trial for several months. At operation the fistulous tract was dissected and excised and the opening in the bowel was closed by intraperitoneal or extraperitoneal methods. Short-circuiting operations or resection of the bowel were at times necessary.

Mayo and Schlicke in 1941 reviewed the records of 155 cases of external fecal fistula encountered at the Mayo Clinic in the five-year period, 1930 through 1934. Nine of the fistulae resulted from diverticulitis. Six patients were operated on with a mortality rate of 16.7 per cent. Treatment, they believed, should be nonsurgical for several months in order to give the fistula adequate chance to heal spontaneously. Mora in 1944 noted that in diverticulitis, fistulae of the anterior abdominal wall always followed spontaneous rupture or surgical drainage of an abscess and that the fistulae frequently closed spontaneously. He expressed a belief that if such did not occur, colostomy should be performed. If they still persisted, excision of the fistulae and resection of the bowel was recommended.

In 1944 Lichtman and McDonald reported on 590 fecal fistulae seen at the clinic from 1930 to 1941. In 408 of these cases operation was performed. Diverticulitis was the underlying lesion in 28, or 6.8 per cent, of the cases. There was recurrence of the fistula after attempted repair in 31 per cent of the cases of diverticulitis. They found that fistulae failed to heal spontaneously because of active disease in the bowel, the presence of foreign bodies, such as cotton fibers and magnesium silicate, or the large size of the fistulous opening in the bowel. Dixon and Benson in 1946 reported a series of 65 consecutive patients with external fecal fistulae who were operated on by Dixon in the three-year period from January, 1942, through December, 1944. In 12, or 18.4

per cent, the fistula was due to diverticulitis. They advised that in perforative diverticulitis with formation of fistula, a preliminary transverse colostomy should precede any attempt at resection by at least three to twelve months.

MATERIALS AND METHODS

Forty-six cases of diverticulitis of the sigmoid colon in which there were bladder or cutaneous fistulae and in which a segment of colon had been removed surgically at the clinic were used for this study. This discussion concerns only 17 cases in which sigmoidocutaneous fistulae occurred. The cases of sigmoidovesical fistulae are being reported elsewhere. The clinical record of each case was carefully reviewed and abstracted on a specially prepared card. The surgically removed tissues which had been fixed and preserved in formalin solution were examined grossly and roughly sketched. Each specimen was sectioned, and blocks of tissue were removed from selected parts for microscopic study. The blocks of tissue were fixed in paraffin and cut, the sections were mounted on slides and stained with hematoxylin and eosin. The sections were studied microscopically, and the changes in the various layers of the wall of the bowel were observed and recorded.

Originally, the clinical records in 25 cases were abstracted, but those in which only colostomy or repair of a fistula was done and no tissue was available for study were excluded from this series. In some instances the surgically removed tissue was not suitable for study. Consequently, this was not a study of 17 consecutive cases of diverticulitis with sigmoidocutaneous fistulae.

The original plan was to study more in detail the fistulous tracts, but in most specimens no tract could be identified. Therefore, in most instances the excised segment of bowel was all that was available for study.

PATHOLOGIC FINDINGS

In each of the 17 cases studied, there was a sigmoidocutaneous fistula. Three of these patients had coexisting enterocolic fistulae, and three had sigmoidovesical fistulae. The length of the excised segment of colon averaged 14 cm for the 17 cases. Characteristically, the involved segment of colon was thickened and rigid and contained multiple diverticula. Areas of abscess formation, granulation tissue, necrosis, and perforation were seen. Fistulous tracts were identified. Microscopically, mucosal ulceration was observed. In areas the entire bowel wall was replaced by a chronic proliferative inflammatory process characterized by the presence of dense fibrous connective tissue, lymphocytes and plasma cells. Frequently, a foreign body granulomatous type of reaction with large, multinucleated giant cells was seen (Fig 1a). Other features were abscesses, hyalinization of muscle and occasionally hypertrophy of the myenteric plexus. The fistulous tracts were lined by inflammatory granulation tissue (Fig 1b) except occasionally where a long diverticulum formed a portion of the tract. Generally the pattern of the tract conformed to that described by Lichtman and McDonald in 1944.

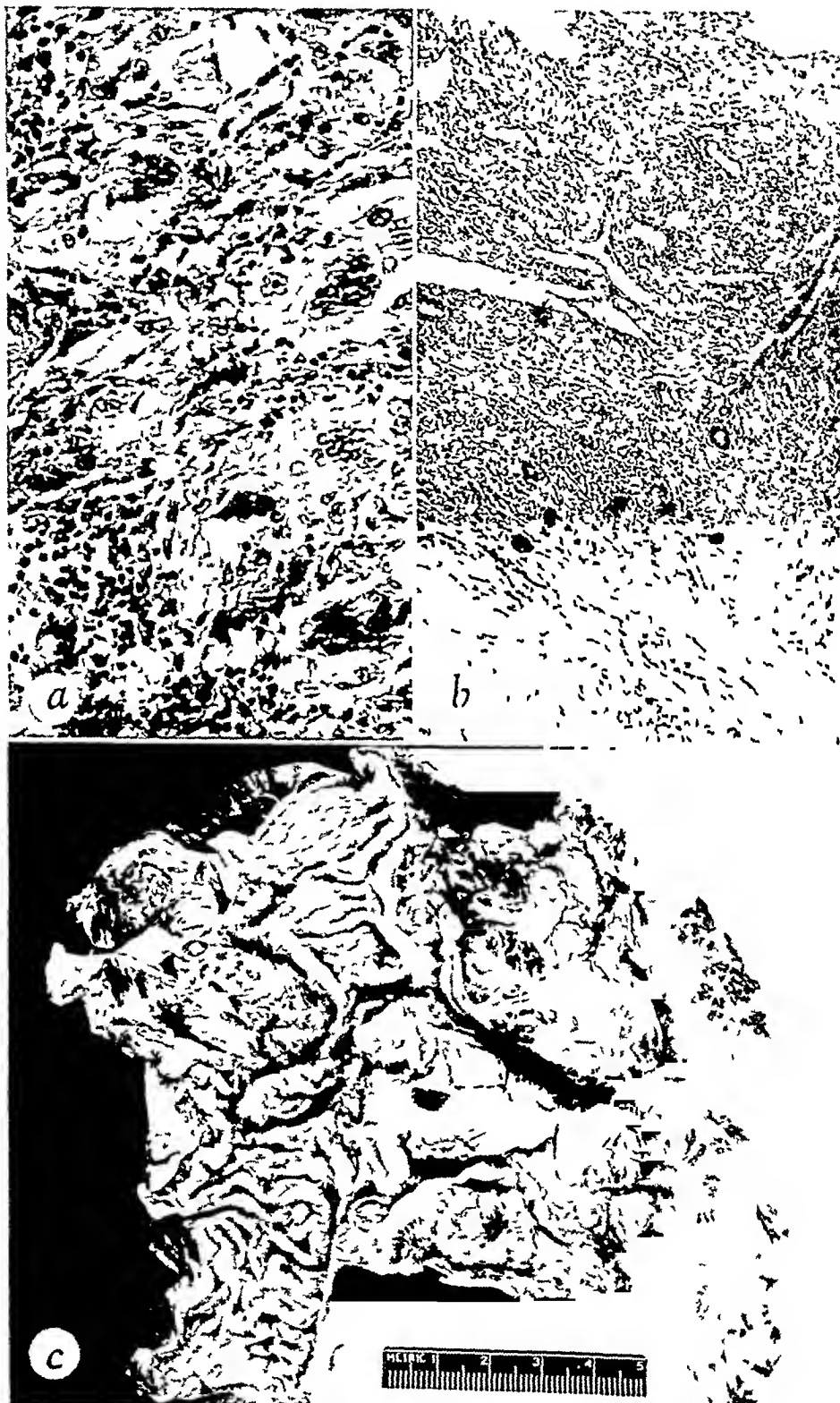


FIG 1a—A foreign body type of granulomatous reaction in perforative sigmoidal diverticulitis (hematoxylin and eosin, $\times 170$)
b—The wall of a sigmoidocutaneous fistulous tract. All tracts had essentially the same appearance (hematoxylin and eosin, $\times 42$)
c—A sigmoidocutaneous fistula

CLINICAL DATA

Sex and age—Twelve of the 17 patients in this group were males. The youngest patient was 27 years old and the oldest 60. The average age was 46.3 years.

Symptoms—All these patients had fistulae which at times drained feces, gas and pus. Pain was the most common symptom and was located in the lower left or midpart of the abdomen usually. Approximately half the patients had had recurrent episodes of chills or fever or both. Commonly, the pain and fever recurred when the fistula closed spontaneously, but relief was afforded when the tract drained again. Constipation was a frequent complaint, but diarrhea was not complained of by any of the patients. In none of the cases was obstruction of the bowel of any clinical significance.

Previous surgical treatment—Fourteen of these patients at some time had had an acute suppurative process within the abdomen, and in each case a sigmoidocutaneous fistula followed surgical drainage of the suppurative lesion. In the other three cases the fistula had followed surgical intervention for the correction of sigmoidovesical fistula. In one of these operations had been performed at the clinic three years previously. Also, in one of these three cases segmental resection of the colon had been done while in the other two, repair of the fistula had been done. In two instances attempts to repair the sigmoidocutaneous fistula were unsuccessful. Exploratory laparotomy was performed in two instances, and in one colostomy and subsequent closure of the colic stoma were done.

Physical findings—In each case the cutaneous opening of the fistula was in the abdominal wall. There was a single opening in 14 of the cases and multiple openings in three. The location in each case was determined by the site of the surgical incisions. In only two instances was there a palpable mass within the abdomen, and one of these masses could be felt through the rectum. If these patients had been seen during the acute stage of the disease, probably all would have had a palpable mass.

Roentgenologic examination of the colon was done in 15 cases preoperatively. In 14 of these a diagnosis of diverticulitis or diverticulosis or both was made. In one instance the lumen of the bowel was obstructed. Fistulous tracts could be seen arising from the sigmoid frequently. In 14 instances proctosigmoidoscopic examination was done. Decrease in the mobility of the bowel was the most common finding, being present in over half the cases. Diverticula were seen in two. In four cases the bowel appeared normal.

Associated fistulae—Six of these patients also had coexisting internal fistulae. Three had enterocolic fistulae and three had sigmoidovesical fistulae. An enterocolic fistula was suspected when food passed rapidly through the intestinal tract. The diagnosis was established by means of roentgenologic examination of the colon with the aid of barium, and in one instance the communication was found at surgical exploration when it had not been suspected previously.

Surgical treatment at the clinic—Eighteen segmental resections of the

colon were done for sigmoidocutaneous fistulae in 17 patients with diverticulitis. An extraperitoneal type of resection was done in 12, or two thirds of the cases. Six of these had a preliminary colostomy. Resection with primary end-to-end anastomosis was done in six, or one third of the cases. Of these, five had a preliminary colostomy. The shortest interval of time elapsing between the performance of the colostomy and resection was 15 months, and the longest interval was 11 months. The average interval was 7.1 months. Fistulectomy was done three times in two cases.

Result of treatment—There were no postoperative deaths. Sixteen of the 17 patients were cured of their cutaneous fistulae. Reoperation was necessary in three patients since a fistula persisted after the initial procedure. An extraperitoneal resection was followed once by the occurrence of a cutaneous fistula which closed spontaneously after a second colostomy and subsequent closure of the colic stoma. A fistulectomy was done twice in one case. The fistula persisted. The patient was cured by a resection and remained well. In the third case in which reoperation was necessary, a fistulectomy and two segmental resections of the bowel were done before all the fistulae were closed. One patient still had a sigmoidocutaneous fistula after segmental resection. Only one patient was left with a permanent colic stoma.

COMMENT

Diverticula of the colon occur most commonly in people above 40 years of age. Males are affected more often than females, the ratio being about 3:2. The pelvic colon is most often the site of involvement, and by far the majority of complications resulting from diverticula occur in the sigmoid. It is not the purpose of this paper to discuss the controversial points regarding the etiology of diverticula. It is the opinion of most authorities that diverticula form as the result of several factors, the most important of which is increased intraluminal pressure plus weakness in the musculature of the bowel wall produced by the penetration of the wall by blood vessels and possibly fat.

The wall of a diverticulum is composed of atrophic mucosa, submucosa and serosa. Not infrequently, a thin layer of muscle is present, especially near the proximal end of the sac. Fecal concretions which are contained within these sacs cause mucosal erosion and irritation, permitting bacterial invasion of the wall of the sac. The inflammatory process initiated by the invading bacteria and toxins occludes the mouth of the diverticulum and produces necrosis and extension of the process into the adjacent wall of the bowel. The severity of the inflammation depends upon the virulence of the organism and resistance of the patient.

If the process spreads rapidly, there is necrosis of the diverticulum and wall of the bowel, perforation and abscess formation. The abscess may attach itself to the abdominal wall, bladder or other viscus and erode through the wall of the viscus, producing a fistula. More commonly, the process spreads more slowly. The bowel wall and the mesentery then become involved in a chronic proliferative extramucosal inflammatory process which Wilson¹³ in 1907 called "peri-

diverticulitis." This is the most important pathologic condition resulting from diverticula. The involved loops of bowel become attached to the abdominal wall or viscera, and abscesses form within the inflammatory mass from time to time and drain through the path of least resistance. Frequently, this path of drainage is into the colon, but not infrequently it is into the bladder, small bowel or abdominal wall. This seems to be the mechanism at work in most of the cases in this group.

In at least four cases a long perforated diverticulum was attached to the abdominal wall and formed an abscess which was drained, leaving a suppurative saccular sigmoidocutaneous fecal fistula (Fig 1c) as described by Lichtman and McDonald in 1944. The proximal part of the fistula was composed of the diverticulum itself, the distal portion was a tract lined with fibrous granulation tissue and connecting the two was an abscess cavity. However, in most instances the bowel had become densely adherent to the abdominal wall and the communication had occurred through the inflammatory mass.

Diverticulitis is an important but not the most common cause of external fecal fistulae. Ginzburg showed that diverticulitis accounted for 3.2 per cent of external fecal fistulae. Lichtman and McDonald found diverticulitis to be the underlying cause in 6.8 per cent of their cases. Dixon and Benson reported diverticulitis to be the cause in 18.4 per cent.

When the patients in our series were first seen at the clinic symptoms had been present on the average, for 46.1 months and the fecal fistula had been present an average of 17.1 months. Thus it is seen that the symptoms of diverticulitis had been present an average of 29 months when the fistula developed. The fact that 14 of these 17 patients had had surgical drainage of an acute suppurative process within the abdomen is evidence that the formation of a fistula in diverticulitis is preceded by the formation of an abscess in most instances. Acute perforation of a solitary diverticulum has been discussed by many authorities, but such is not the usual mechanism of the formation of a fistula. Surgical trauma is a contributing factor in many cases. Not all external fecal fistulae caused by diverticulitis have their openings in the anterior abdominal wall. They may open in the lumbar region, buttocks, thigh, perineum, thorax or perianal region. In the present group, all openings occurred in the abdomen, with most of them located in the lower midline or to the left of it. In none of these cases could the opening into the sigmoid be visualized on proctosigmoidoscopic examination.

To determine the underlying cause and the part of bowel from which an external fistula arises is at times a difficult task. The history and physical examination are helpful, but the most valuable information is afforded by roentgenologic examination of the colon. In the present group, a diagnosis of diverticulitis or diverticulosis or both was made in all cases except one in which the lumen of the bowel was obstructed. In almost half the cases a fistulous tract could be seen to arise from the sigmoid. In some instances roentgenologic examination after the injection of iodized oil into the tract revealed the site of origin of the fistula.

As shown by Mayo and Schlicke, and by Rankin, Baigen and Buie, the basic lesions from which fecal fistulae result are numerous. The commoner ones which must be considered in the differential diagnosis are appendiceal disease, regional enteritis, tubo-ovarian inflammatory disease, pelvic or intestinal tuberculosis, malignant tumors of the pelvis or bowel, ulcerative colitis, actinomycosis, traumatic perforation of the bowel and foreign body. Fecal fistula may follow various intra-abdominal operations.

As emphasized by Jones,⁸ Mayo and Schlicke, and Dixon and Benson, external fecal fistulae resulting from diverticulitis tend to heal spontaneously, and ample time, perhaps a year, should be allowed for healing to occur before surgical measures for correction are employed. Fourteen of the 17 patients in our series had had their fistulae a year or longer before they were treated surgically at the clinic. The other three were operated on two, five and seven months respectively after development of the fistulae.

For the correction of sigmoidocutaneous fistulae that result from diverticulitis, any surgical procedure less radical than segmental resection of the diseased bowel usually fails. This has been emphasized by various authorities. Dixon and Benson expressed the belief that a preliminary colostomy should precede resection by three to 12 months, while Babcock (1945) has followed the practice of doing a resection and primary anastomosis without colostomy. It would seem that the type of procedure chosen should depend entirely upon the conditions presented in the individual case. Usually it is safer to establish a preliminary transverse colic stoma and after an interval of a few months to carry out a resection and end-to-end anastomosis or an extraperitoneal resection, subsequently closing the colic stoma. However, at times in perforative diverticulitis, it seems advisable to do a primary resection and end-to-end anastomosis with or without simultaneous transverse colostomy.

Eleven of the 17 patients were prepared preoperatively with the aid of succinylsulfathiazole (sulfasuxidine), and in most instances one of the sulfonamides was used intraperitoneally.

SUMMARY AND CONCLUSIONS

A review of the literature on diverticulitis with sigmoidocutaneous fistulae has been presented. According to various investigators diverticulitis accounts for 3.2 to 18.4 per cent of the external fecal fistulae. Our work was based upon 17 cases of sigmoidocutaneous fistula due to diverticulitis of the sigmoid colon. In each case a segmental resection of the colon was done at the Mayo Clinic. Characteristically, the excised segment of the colon presented many diverticula. The wall of the bowel was involved in a chronic extramucosal proliferative inflammatory process. Commonly, areas of necrosis, abscess formation and perforation were seen. As with colonic diverticula, fistulae were more common in older than in younger men.

The symptoms of sigmoidocutaneous fistula were the presence of the fistulae, abdominal pain, constipation and chills and fever. Each fistula followed some type of surgical operation, usually incision and drainage for an acute suppur-

ative process within the abdomen. These patients had had symptoms suggestive of diverticulitis for an average of approximately 2.5 years when their fistulae developed. The fistulae had been present for an average of approximately 1.5 years when the patients came to the clinic. Roentgenologic examination of the colon was the most important aid in diagnosis and differential diagnosis. Other types of internal fistulae were present in about one-third of the cases.

Fistulae of this type tend to close spontaneously and should be allowed ample time, approximately 12 months, to do so. When surgical treatment is carried out, excision of the diseased segment of colon should be done and should usually be preceded by a temporary transverse colostomy made six months prior to resection. The choice of procedure should depend on the conditions present in the individual case. In this group of 17 patients with sigmoidocutaneous fistulae there were 18 segmental resections of the colon with no operative deaths. Sixteen patients were relieved of their external fecal fistulae.

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A NEUROGENIC FACTOR IN EXPERIMENTAL TRAUMATIC SHOCK A SUMMARY OF RECENT STUDIES INCLUDING OBSERVATIONS ON PROCAINIZED AND SPINAL DOGS*†

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THE PURPOSE OF THE PRESENT REPORT IS to correlate and integrate a series of investigations carried out between 1942 and 1947 to determine the role of the afferent nervous factor in experimental traumatic shock

During World War I, it was found that in a group of 27 soldiers suffering from wound shock,¹ the total blood volume was reduced, and that the reduction in volume bore a definite relation to the severity of the clinical state of the patient. The question that remained to be answered is whether or not, in these forms of shock, the complete traumatic syndrome can always be accounted for by the loss of circulating blood volume alone. The investigations to be described were undertaken to elucidate this point.

Cannon and Bayliss² were the first group of investigators to estimate the loss of fluid into an injured part after traumatizing the muscles of one thigh of the cat. They determined the amount of bleeding by removing the two hind limbs by symmetrical cuts across the thighs and weighing them. They stated that there was not sufficient bleeding into the wounds to account for the effects observed. Again, in a later series of experiments, Cannon³ found that in some cases the difference in weight of the two sides was as low as 11 per cent of the estimated weight of the total blood of the animal and concluded that the development of the low blood pressure after tissue injury was proved not to be due to fluid loss from the systemic circulation. In 1930, Blalock⁴ and Parsons and Phemister⁵ repeated the observation on dogs with amputation in the mid-abdominal region instead of across the thighs. The difference in weight between the two halves was found to vary from 42 to 80 per cent of the body weight with an average of 51 per cent in a group of eight dogs reported by Blalock, and from 42 to 60 per cent with an average of 53 per cent in the series of six dogs reported by Parsons and Phemister. These results indicate that severe muscle trauma to a thigh results in some bleeding and accumulation of fluid in the loose tissue of the groin and flank, which is not included in the amputated parts if the incision is made across the upper edge of the thigh. The evidence advanced by these investigators suggests further that in *severe* muscle

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trauma the local loss of blood and fluid may be sufficient of itself to precipitate fatal shock. Unfortunately, they made no direct measurements of blood volume changes. Furthermore, these experiments were carried out on anesthetized animals, in which all compensatory mechanisms in response to injury and blood loss are modified to a considerable extent^{6, 7}. At any rate, the important question which remained unanswered is whether or not the amount of bleeding incidental to a *moderate* degree of muscle trauma is also adequate to account for the ensuing fatal syndrome.

Actual determination of the reduction of blood volume in various types of shock has been made by a number of workers^{1, 8}. But the methods have not been of sufficient accuracy to permit a quantitative study of blood loss in traumatic shock. Recently, Gregersen and his associates made a careful study of the dye (T-1824) dilution method in normal, hemorrhaged and traumatized dogs⁹ as well as in the human patients^{10, 11}. They found that the blood volume

TABLE I—Data on dogs with blood volume reduction as a result of (a) simple hemorrhage, (b) muscle trauma, (c) sublethal hemorrhage plus sciatic stimulation, and (d) muscle trauma and chronic deafferentation (abstracted from Wang, et al^{14, 28, 42})

	Hemorrhage	Muscle Trauma	Hemorrhage Plus Stimulation	Deafferentation and Trauma
Control blood volume (cc/kg)	97.9 ± 1.3	100.7 ± 1.5	96.7 ± 1.5	99.1 ± 1.5
Residual blood volume at 50% mortality	59.1 ± 2.9	73.4 ± 3.0	69.0 ± 2.5	64.7 ± 1.8
Percentage survival at 66 cc/kg residual volume	76 ± 8.7	25 ± 8.3	37 ± 9.5	59 ± 10.8

determined with the dye method checked within 5 per cent of the value obtained with the improved CO method¹². Using this standardized dye dilution method, Wang, et al^{13, 14} compared the effects of reducing the circulating blood volumes in dogs by simple hemorrhage or by muscle trauma. They reported a striking difference in the ability of these two groups of animals to withstand a specific loss of blood. In dogs in which the blood volume is reduced to 66 cc per kg by simple hemorrhage the percentage survival is 76 ± 8.7 per cent, if, on the other hand, a similar reduction is effected by muscle trauma, the chance of survival is only 25 ± 8.3 per cent (summarized in Table I). Hemorrhaged animals have a 50 per cent mortality if the blood volume is reduced to 59.1 ± 2.9 cc per kg, whereas in muscle trauma the same chance of survival prevails when the residual volume is 73.4 ± 3.0 cc per kg*. This difference in the ability of the two groups of animals to withstand blood loss could not be ascribed to the constant leakage of blood and fluid into the injured area since the blood volume remains fairly constant throughout the period of observation⁹. Indeed, if water is given to the animals six hours after trauma, the total circulating volume on the following day is not significantly altered from that determined two hours after injury¹⁴. Therefore, the evidence clearly indicates

* The concept of selecting a 50 per cent mortality point and comparing the effect of the two procedures is an important one, for severe muscle trauma that produces a 100 per cent mortality may conveniently result in an extensive blood loss comparable to that observed in animals suffering from fatal hemorrhage.

that the ability of hemorrhaged dogs to withstand a critical quantity of blood loss is strikingly greater than that of dogs receiving muscle trauma. This fact was the basis for undertaking further investigation of other possible factors contributing to the high mortality rate in traumatized animals.

As illustrated in Figure 1, the traumatized animals as contrasted with hemorrhaged animals have early tachycardia exceeding 200 beats per minute, high mean blood pressure, high hematocrit values, and early depression of the central nervous system. They also showed high calculated peripheral resistance¹⁵ and prolonged fluorescein circulation time¹⁶. These differences suggest

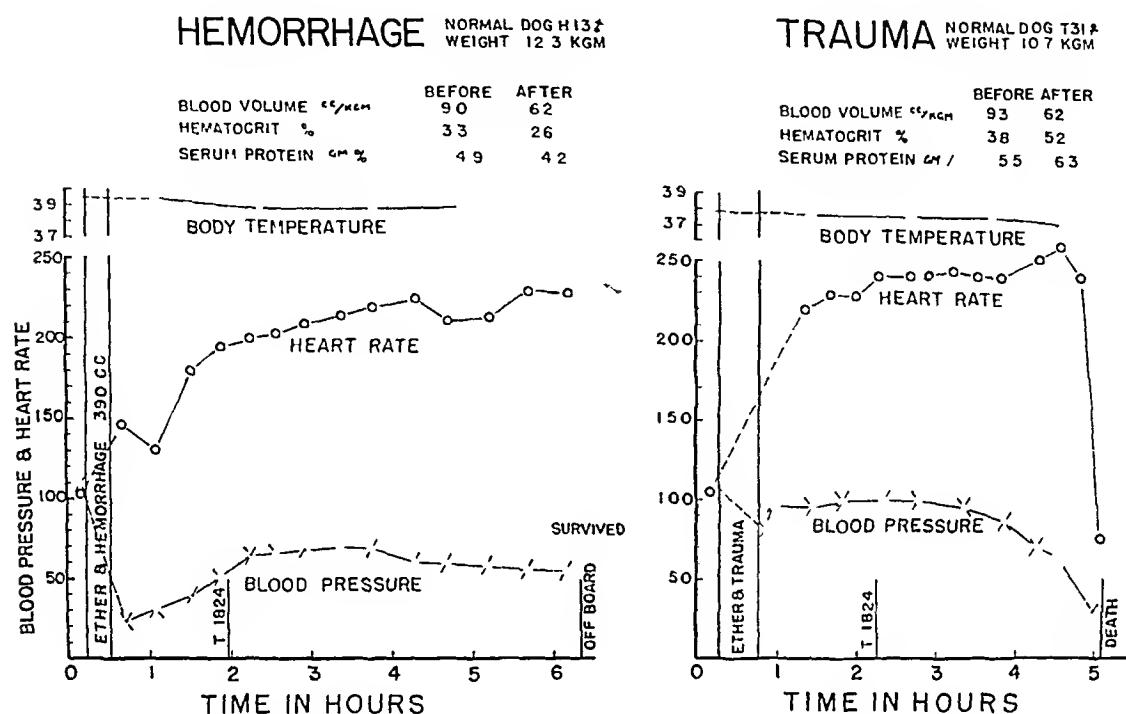


FIG 1—Comparison of the clinical manifestations in a typically hemorrhaged animal (dog H 13) and a typically traumatized animal (dog T 31). Note the characteristic slowly increasing tachycardia and low mean blood pressure level in the hemorrhaged animal which survived. The traumatized animal, despite its high (nearly normal) blood pressure level, died after 4 hours (from Wang, *et al*¹⁴).

that the sympathetic nervous system is intensely active in traumatic shock. The question arises as to whether or not intense sympathetic activity can be initiated by afferent impulses from the injured areas.

Slome and O'Shaughnessy¹⁷ have shown that shock can be produced in the cat by appropriate trauma to the perfused limb separated completely from the general circulation and communicating with the body only by means of its nerves. Such a finding, though confirmed by Lorber, Kabat and Welte,¹⁸ is not substantiated by Bell, Clark and Cuthbertson,¹⁹ nor by Blalock and Cressman.²⁰ In any case, it is difficult to evaluate this type of experiment because it must be done under deep narcosis. On the other hand, a number of investigators^{21, 22, 23, 24} have stimulated the sciatic or other somatic afferent nerves in unsuccessful attempts to produce a depression of blood pressure and shock.

Recently, Phemister and his associates^{25, 26} stimulated the sciatic nerves in rabbits under urethane and in dogs under sodium barbital and obtained only pressor responses

Statistical evaluation of the quantitative data on uncomplicated hemorrhage¹⁴ enabled this laboratory to ascertain the ability of animals to withstand hemorrhage and thus to carry out a series of sublethal hemorrhage experiments coupled with continuous electrical stimulation of the sciatic nerves^{27, 28} The stimulation was started immediately after hemorrhage while the animals were still under the residual effects of ether anesthesia The mean blood pressure showed a large increase at first which is probably related to struggling Within a minute or two, the blood pressure returned to a level 25 to 35 mm Hg above the reading taken immediately before stimulus was applied The heart rates were maintained over 200 beats per minute In most instances these effects

TABLE II—Comparison of changes in hematocrit values and plasma protein concentrations in dogs following (a) simple hemorrhage, (b) muscle trauma, (c) sublethal hemorrhage plus sciatic stimulation, and (d) muscle trauma and chronic deafferentation (abstracted from Wang, et al^{14, 28, 42})

	Hemorrhage		Muscle Trauma		Hemorrhage Plus Stimulation		Deafferentation and Trauma	
	Hct %	Protein Gm %	Hct %	Protein Gm %	Hct %	Protein Gm %	Hct %	Protein Gm %
Control values	41.9	5.8	42.9	5.8	44.7	5.7	40.5	6.1
s e	1.1	0.1	0.9	0.1	1.0	0.1	0.9	0.1
Changes after injury	-4.8	-0.9	4.1	0.0	-1.7	-0.5	1.7	-0.5
s e	0.8	0.06	0.9	0.07	0.7	0.05	0.7	0.05

persisted, for if the stimulus was suddenly discontinued at any time during the experiment both blood pressure and heart rate slowly decreased In this series of experiments with sublethal hemorrhage plus stimulation, the average quantity of blood removed is 33 cc per kg, which is considerably smaller than that in the simple hemorrhage series (40 cc per kg), and the residual blood volume at the 50 per cent mortality point is 69.0 ± 2.5 cc per kg, which is significantly higher than the corresponding value in the simple hemorrhage series (59.1 ± 2.9 cc per kg, see Table I) The percentage survival at a residual volume of 66 cc per kg in this series (37 ± 9.5 per cent) is also significantly different from that in the simple hemorrhage series (76 ± 8.7 per cent) Thus, it is apparent, that at any given blood volume reduction, the ability of the animal suffering simple hemorrhage to survive is significantly greater than either (a) the dog suffering muscle trauma or (b) the dog suffering a sublethal hemorrhage and afferent nerve stimulation

The data indicate clearly that strong sciatic stimulation plays an important role in elevating the mortality rate in animals with reduced blood volume However, in normal animals electrical stimulation of the sciatic nerves has little effect, certainly it alone will not produce shock Indeed, we have not been able by afferent nerve stimulation to put any dog with a residual blood volume over 75 cc per kg into fatal shock

The clinical signs observed in the animals of the nerve stimulation series were similar to those shown by traumatized animals: early tachycardia (over 200 beats per minute), relatively high mean blood pressure, early central nervous system depression and sudden death with a sharp decline of blood pressure (Fig 2). It may appear paradoxical that increased blood pressure following sciatic stimulation exerts a deleterious effect upon the condition of the hemorrhaged animal. Indeed, in our experience the animals that give the most marked sciatic pressor responses are those that show an early depression of the central nervous system and death. In an animal with an already reduced blood volume, the cardiac output is decreased and the tissues anoxic. If, through sciatic stimulation, the vessels are further constricted despite the resulting high blood pressure there will be a further reduction of peripheral blood flow, tissue damage and death. The failure of previous workers to produce shock by afferent nerve stimulation can be accounted for by the following facts that they (a) used anesthetized animals in which the metabolism and vasomotor reflexes are depressed, (b) did not use animals with a slightly reduced blood volume, and (c) expected an immediate depressor response following electrical stimulation of the somatic afferent nerves.

It has long been known that nearly all anesthetics depress vasomotor reflexes. In fact, as early as 1918, Wiggers²⁴ in his studies on shock remarked, "It seems probable that the potency of peripheral stimuli and trauma in producing reactions in the body leading to shock and circulatory failure depends, to a considerable extent, on how little the conducting mechanisms of the spinal cord and brain are depressed by the anesthetic." And yet all investigators who attempted to produce shock by stimulation of the afferent nerves have given various anesthetics to the animals, perhaps in the belief that unanesthetized animals would be unmanageable if the afferent nerves were stimulated. In our

HEMORRHAGE NORMAL DOG S21 WITH AFFERENT NERVE STIMULATION WEIGHT 9.0 KGM

	BEFORE	AFTER
BLOOD VOLUME, cc/KGM.	90	63
HEMATOCRIT, %	42	43
SERUM PROTEIN gm %	6.8	6.3

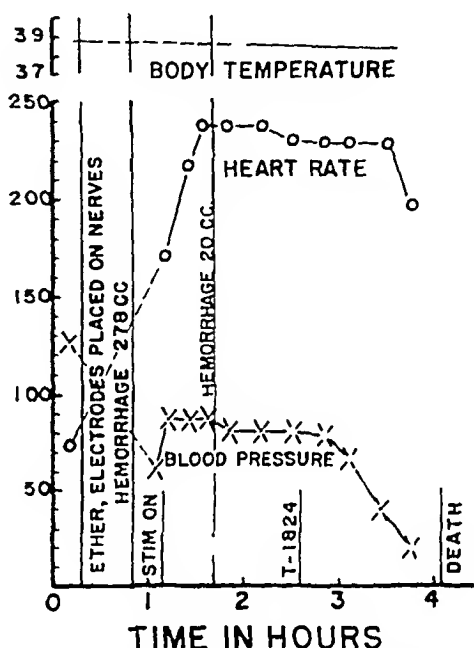


FIG 2—The clinical manifestations of a dog (S 21) which has been subjected to hemorrhage and stimulation. The blood volume reduction is comparable with that in dog H 13 and dog T 31. Note the effect of stimulation of the sciatic nerves on the heart rate and mean blood pressure. This figure demonstrates the similarities between this dog and the traumatized dog (T 31) in early tachycardia exceeding 200 beats per minute, high level of mean blood pressure and death with a rapid decline of the pressure (from Overman and Wang²⁸).

experience, except for initial struggling, the animals remained quiet, though the effect of reflex nociception was clearly maintained. Expressions of pain could easily be obtained again if the stimulus were reinstituted after being briefly discontinued. In view of the fact that pain receptors are believed to be slow adapting,²⁹ the early disappearance of this sensation in these animals must be presumed to be central. In this connection, it is interesting to note that severe wounds in soldiers are often associated with little pain, even though they are not in shock at the time.³⁰

Investigators have not previously attempted to produce shock by combining hemorrhage and somatic afferent nerve stimulation. One of the difficulties has been the failure to recognize that even an important contributing nervous factor to the development of shock might not alone be expected to produce a fatal outcome. It is, however, well known that fluid loss, important as it is, may not alone produce fatal shock. Once this fact is recognized, the production of shock becomes a quantitative matter and the precipitating factors may well be present each alone in sublethal quantity, the algebraic sum being sufficiently deleterious to lead to death. A second difficulty faced by previous investigators has been in the estimation of the degree of hemorrhage which is sublethal. It is interesting that Mann²³ has said, "It is impossible to reduce the anesthetized animal to a state of shock by any degree of sensory stimulation provided all hemorrhage is prevented." Phemister and his associates²⁷ hemorrhaged animals to shock levels of blood pressure and then superimposed a further fall of blood pressure by aortic depressor nerve stimulation. They likewise stimulated the sciatic nerves in anesthetized rabbits and dogs, and failed to obtain a fall in blood pressure throughout a period of one or more hours of stimulation. Having failed to find the anticipated depressor response to sciatic stimulation, they did not proceed to combine stimulation and hemorrhage.

Recently Triueta, *et al*^{31, 32} reported a diversion of the intra-renal blood flow from the cortex to the medulla, with a subsequent variable cortical ischemia, as a result of hemorrhage, muscle trauma, or stimulation of the central end of the divided sciatic nerve. This information is interesting because it shows that sciatic stimulation may produce a change in renal circulation identical to that produced by hemorrhage or muscle trauma. Further, the resulting ischemic kidney tissue might contribute one or more chemical factors in addition to the nervous pressor effect of somatic afferent stimulation.³³ However, the importance of these newly discovered phenomena in the shock syndrome has yet to be ascertained.

Although afferent nerve stimulation in sublethally hemorrhaged dogs produces alterations in mortality rate and in the clinical signs of shock which bring such animals into close resemblance with traumatized dogs, these experiments are open to certain criticisms. First, exposure of the sciatic nerves entails a certain amount of trauma and secondly, electrical stimulation is a highly artificial stimulus. Therefore, it is pertinent to make as a corollary the following observation, *ie*, the effect of deafferentation on the course of traumatic shock to show if traumatized deafferent animals have a mortality rate

and a clinical shock syndrome similar to hemorrhaged animals. Many workers have attempted to interrupt the pathways which carry nociceptive impulses centrally from the region of injury,^{34, 35, 36, 37, 38, 20} but most of them also have used general anesthesia. The results have been diversified and often conflicting. Swingle and his associates^{37, 38} have studied the effect of exclusion of the afferent impulses in traumatic shock and have reported that many deaths are prevented by local procaine anesthesia. However, one is forced to accept these results with reservations for there is no adequate objective proof that the severity of injury was exactly the same as in the control experiments. The criterion used was to traumatize the animals until the mean blood pressure was reduced to 70 mm Hg or lower. Since the afferent impulses yield, as we believe, a reflex pressor effect instead of a depressor response, trauma given to the procainized hindlegs which results in a fall of blood pressure to 70 mm Hg

TABLE III—Data on traumatized dogs in which the hindlegs have been infiltrated with procaine (4 per cent solution), including changes in blood volumes, hematocrit values and plasma protein concentrations

Dog No and Sex	Body Wt kg	Control			After Muscle Trauma			Change			Fate
		B V cc /kg	Hct %	Prot Gm %	B V cc /kg	Hct %	Prot Gm %	B V %	Hct %	Prot Gm %	
P 1 ♀	10.0	126	45.0	5.8	92	46.7	6.0	27	1.7	0.2	Survived
P 2 ♂	9.4	113	55.0	5.5	85	55.0	5.4	25	0.0	-0.1	Died, 3.7 hr
P 3 ♀	12.4	121	49.1	6.6	81	51.9	6.5	33	2.8	-0.1	Died, 6+ hr
P 4 ♀	7.9	100	48.2	5.5	76	50.4	5.4	24	2.2	-0.1	Survived
P 5 ♂	8.8				75	52.0	5.5				Died, 6+ hr
P 6 ♂	16.8				74	45.7	6.5				Survived
P 7 ♂	12.4	104	49.6	5.5	66	44.6	5.0	37	-5.0	-0.5	Died, 5.3 hr
P 8 ♀	11.1	102	47.9	6.1	64	48.2	5.2	37	0.3	-0.9	Died, 5.2 hr
P 9 ♀	11.0	94	39.0	5.7	63	38.1	5.3	33	-0.9	-0.4	Died, 2.7 hr
P 10 ♀	9.2	111	44.1	6.1	63	42.7	5.3	43	-1.4	-0.6	Died, 6+ hr

is generally not as severe as that which results in a similar fall of blood pressure in a non-procainized animal. We have, therefore, repeated these experiments including measurement of control and residual blood volumes in an effort to standardize the degree of blood loss (Table III). The procedure involved in local procaine infiltration is simple. Furthermore, procaine is an ideal drug since in suitable doses it selectively blocks impulses in the pain fibers.³⁹ On the other hand we often experience difficulty in deciding upon the dosage to be given and it must likewise be apparent that procaine in large doses may have some undesirable side effects on the neuro-circulatory system of traumatized animals.

With these reservations in mind, a review of our series of procainized traumatized dogs reveals that although several of these animals showed less excitement during the period of incipient shock and slower heart rates compared with the untreated animals in traumatic shock, the chances of survival for these procaine-treated animals were not enhanced when the blood volume was reduced to the same extent as in the non-procainized controls.

In another series of experiments it was found that sectioning the spinal cord at the level of T₁₀₋₁₂ following muscle trauma did not benefit the animals (Table IV). Swingle and co-workers³⁸ were similarly impressed by data on dogs transected just previous to the trauma procedure. In the series reported here, several animals died so soon after the transection that there was insufficient time for a second blood volume determination. It appears then that acute spinal transection is too drastic a procedure for traumatized dogs to withstand. In a third series of experiments, chronic spinal animals were used.* Again it was found that death following muscle trauma is not prevented in such preparations (Table V). The difficulty has been that spinal animals are not able to micturate adequately by themselves and are prone to develop cage sores. Consequently, most of the muscle trauma experiments were carried out in the first

TABLE IV—Data on traumatized dogs in which the spinal cord was severed at the level of T₁₁ following muscle trauma, including changes in blood volume, hematocrit values and plasma protein concentrations

Dog No and Sex	Body Wt kg	Control			After Muscle Trauma			Change			Fate
		B V cc/kg	Hct %	Prot Gm %	B V cc/kg	Hct %	Prot Gm %	B V %	Hct %	Prot Gm %	
TS 1 ♂	11.8	99	40.8	5.9	84	50.8	6.4	15	10.0	0.5	Survived
TS 2 ♂	10.9	109	38.2	7.7	83	39.6	7.4	24	1.4	-0.3	Survived
TS 3 ♀	14.3	122	50.5	6.2	78	48.9	6.0	36	-1.6	-0.2	Died 5.5 hr
TS 4 ♂	16.1	100	42.6	6.4	76	37.3	5.4	24	-5.3	-1.0	Died 2.4 hr
TS 5 ♀	13.0	114	38.8	5.3	75	50.0	5.9	34	11.2	0.6	Survived
TS 6 ♂	13.9	84	51.2	6.2	74	62.8	6.4	12	11.6	0.2	Survived
TS 7 ♂	9.8	100	43.6	5.7	74	47.5	5.7	26	3.9	0.0	Died 6+ hr
TS 8 ♀	7.8	109	57.4	5.6	74	53.3	5.3	32	-4.1	-0.3	Died 2.3 hr
TS 9 ♂	9.0	111	36.2	6.0	74	41.8	6.3	33	5.6	0.3	Died 2.5 hr
TS 10 ♂	8.0	93	35.1	5.3	59	35.5	5.0	37	0.4	-0.3	Died 4.2 hr

postoperative week during which the animals had not fully recovered from the operation, as evidenced by a decrease in body weight (Table V) and a low control blood volume in several of these dogs. Nevertheless, these animals showed a slight degree of tachycardia and low mean blood pressure, and the central nervous system was not depressed until death was clearly imminent (see Fig. 3). In other words, chronic spinal animals presented a shock syndrome following muscle trauma, which was very much like that which occurred in the normal animal with a similar reduction of blood volume by hemorrhage. However, the mortality rate of traumatized spinal animals did not differ significantly from that of traumatized normal animals.

From these series of experiments on acute and chronic cord transection

* This series of experiments (Table V) were performed with the collaboration of Professor Walter S. Root. In several of these dogs, the lumbar sympathetic chains were extirpated approximately 2 weeks before the spinal operation in order to eliminate the visceral afferent fibers in the chains. No differences in symptomatology following muscle trauma were observed in these animals and in animals in which only the spinal cord was transected.

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it may be inferred (a) that acute spinal transection is not a desirable experimental procedure to eliminate afferent impulses from the injured region in traumatic shock and (b) that animals need a longer period than a few days for recuperation from the effects of a major surgical procedure. The operation designed to meet these requirements is a complete deafferentation of both hindlegs, leaving only the three sacral dorsal roots on one side intact to preserve the function of micturition. Although the operation is much more extensive than simple transection of the spinal cord, it has definite advantages in that such animals are deprived only of afferent pathways and their postoperative course is relatively uneventful because voluntary micturition is preserved. The general condition of these animals, at the time of the traumatic procedure, was good as indicated by the normal body weights and blood volume.*

TABLE V—Data on chronic spinal dogs before and after trauma, including changes in blood volumes, hematocrit values and plasma protein concentrations

Dog No and Sex	Body Wt kg	Control			After Muscle Trauma			Change			Fate
		B V cc/kg	Hct %	Prot Gm %	B V cc/kg	Hct %	Prot Gm %	B V %	Hct %	Prot Gm %	
ST 1 ♂	11.1(11.4)*	107†	47.9	5.9	87	48.4	5.9	19	0.5	0.0	Died 5.6 hr
ST 2 ♂	7.5(7.8)	98	52.6	6.4	84	53.6	6.5	14	1.0	0.1	Died 3.1 hr
ST 3 ♀	14.2(14.6)	109	53.5	6.6	82	52.8	6.0	25	-0.7	-0.6	Survived
ST 4 ♀	8.9(10.0)	111	49.1	5.7	79	43.1	5.5	29	-6.0	-0.2	Died 3.8 hr
ST 5 ♂	13.5(14.6)	117	45.3	6.1	73	48.2	6.0	38	2.9	-0.1	Survived
ST 6 ♂	10.7(11.3)	96	43.3	5.9	71	40.8	5.4	26	-2.5	-0.5	Died 4.4 hr
ST 7 ♂	11.7(12.0)	102	52.4	6.4	70	48.4	6.0	31	-4.0	-0.4	Survived
ST 8 ♂	12.6(13.1)	92	45.4	6.0	69	50.0	5.8	25	4.6	-0.2	Died, 5.0 hr
ST 9 ♂	12.8(13.2)	94	40.9	5.8	67	39.0	5.3	29	-1.9	-0.5	Died 2.0 hr
ST 10 ♀	10.6(10.8)	80	40.5	5.8	63	38.9	5.5	21	-1.6	-0.3	Died 3.0 hr
ST 11 ♂	9.4(9.5)	100	37.7	5.7	63	39.4	5.5	37	1.7	-0.2	Died, 6+ hr
ST 12 ♂	13.4(14.0)	84	45.6	6.4	62	45.1	6.1	26	-0.5	-0.3	Died 6+ hr
ST 13 ♂	12.8(13.1)	88	35.0	6.0	61	37.2	5.9	31	2.2	-0.1	Died, 6+ hr
ST 14 ♂	10.0(10.5)	94	42.3	5.9	60	42.6	5.5	36	0.3	-0.4	Died 4.8 hr
ST 15 ♂	8.7(9.0)	79	44.3	6.4	59	44.0	6.3	25	-0.3	-0.1	Died, 2.0 hr
ST 16 ♀	9.6(10.0)	87	48.3	6.9	57	52.6	6.4	34	4.3	-0.5	Died 4.3 hr

* Body weight at time of spinal transection

† The blood volume is calculated on the basis of the body weight at the time of trauma experiment

* Phemister, *et al*⁴⁰ have sectioned aseptically all the dorsal roots on the left side below T₁₂ in 4 dogs. They reported that these dogs tolerated trauma and blood loss in the deafferent region no better than did the normal dogs. Unfortunately, trauma experiments were performed only 4 hours to 6 days after the operation. It is also of interest to note that in 3 out of the 4 dogs, considerable hemorrhage occurred during the deafferentation operation, and that equivalent transfusion had to be given in an attempt to replace the lost blood. However, animals following extensive laminectomy for the exposure and section of all the dorsal roots of a hindlimb need relatively long period for recuperation, since our dogs, despite negligible blood loss during the operation, showed continued weight loss for the next 7 to 10 days and a return to control body weight and control blood volume did not occur until the 4th week, indicating that recovery of these animals could not be attained within a few days.

The results of the trauma experiments which were performed in the deafferent animals have been reported in detail elsewhere^{41, 42} In brief the residual blood volume at the 50 per cent mortality point in this series of 30 dogs is considerably reduced (64.7 ± 1.8 cc per kg, see Table I) as compared with the value in the normal trauma series (73.1 ± 3.0 cc per kg). The difference between these two values is statistically significant. Also the percentage survival at a residual volume of 66 cc per kg in the deafferent series (59 ± 10.8 per cent) is significantly higher than the value in

TRAUMA		DOG ST 6 ♀
WITH SPINAL CORD CUT AT T11		WEIGHT 10.7 KG
	BEFORE	AFTER
BLOOD VOLUME cc/kgm	96	71
HEMATOCRIT %	43	41
SERUM PROTEIN, gm%	5.9	5.4

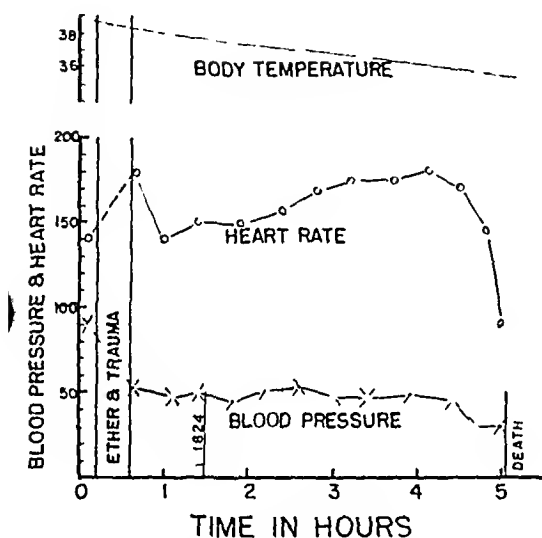


FIG 3.—The clinical manifestations of a chronically spinal transected dog (ST 6) which has been subjected to muscle trauma 6 days after transection. This animal showed a high heart rate, a low mean blood pressure and a loss of 0.6 kg of body weight on the day of trauma experiment. Nevertheless, following muscle trauma, it showed a slowly increasing tachycardia and low mean blood pressure, which are often observed in the hemorrhaged dogs (see dog H 13, Fig 1). But this dog did not survive.

mean blood pressures of less than 70 mm Hg within the first half hour following injury. Six of these survived. On the other hand, in a large series of over 100 muscle trauma experiments on normal animals accumulated in this laboratory only three dogs survived when the initial mean blood pressure was reduced below 70 mm Hg. This suggests that the procedure of muscle contusion has two concurrent effects on the mean blood pressure level: (a) the reduction in circulating blood volume causes a reduction of the mean blood pressure; (b) the local somatic afferent impulses produce an elevation of blood pressure. In some animals the latter effect is so dominant that the blood pressure is higher

the normal trauma series (25 ± 8.3 per cent). Our data indicate clearly that animals survive muscle trauma with a greater reduction of blood volume if the afferent impulses from the injured area are interrupted by previous deafferentation. The afferent impulses from the injured region must have played an important role in bringing about the high mortality of traumatic shock in normal animals.

The clinical picture of the deafferent dogs following muscle trauma (Fig 4), like that shown by the spinal preparation (Fig 3), closely resembles that of simple hemorrhaged animals (Fig 1). As a group, the deafferent dogs had a tachycardia of less than 200 beats per minute or such a heart rate was attained only some time after injury. The deafferent dogs were usually not restless, and were not depressed until immediately before death. In these animals the mean blood pressure was usually very low immediately after muscle trauma. In the series of 30 deafferent dogs 14 had

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after traumatic injury than the control. Although the blood pressure of the traumatized normal animal is higher than that shown by the deafferent dogs in which an equivalent reduction in blood volume has been produced by muscle trauma, the chances of survival of the former group are not any better, indeed, these chances are definitely worse. *It is the quantity of blood flow to the important tissues rather than the blood pressure alone which is the important factor in determining the fate of animals in shock.* Our data again indicate that afferent impulses reflexly excite the sympathetic nervous system and thus may exert a detrimental effect on the traumatized animals by a further reduction of the tissue blood flow, this being the result of increased peripheral vasoconstriction.

Fluid shifts as effected by changes in capillary hydrostatic pressure and reflected in altered hematocrit values and plasma protein concentrations are likewise in agreement with the contention that afferent impulses stimulate the sympathetic nervous system. It has been shown that sciatic stimulation in the sublethally hemorrhaged dog decreases the inflow of fluid into the blood stream and increases splenic contraction (see Table II).²⁸ On the other hand, in traumatized animals in which afferent impulses from the injured area have been excluded, there appears to be a more appreciable fluid shift into the plasma compartment and a lesser contraction of the spleen.^{3,12}

The sympathetic nervous system is stimulated by the buffer nerve mechanism in shock produced either by hemorrhage or by muscle trauma.⁴⁴ It has been shown by Freeman, *et al*.⁴⁵ that a totally sympathectomized animal, though able to tolerate a low pressure for a long time, is not able to withstand an equivalent volume of blood loss as a normal animal. Thus, it is evident that the sympathetic vasoconstrictor effect is a compensatory mechanism, adapting the capacity of the system to the available volume of blood within it. Since additional vasoconstriction is associated with afferent stimulation and since

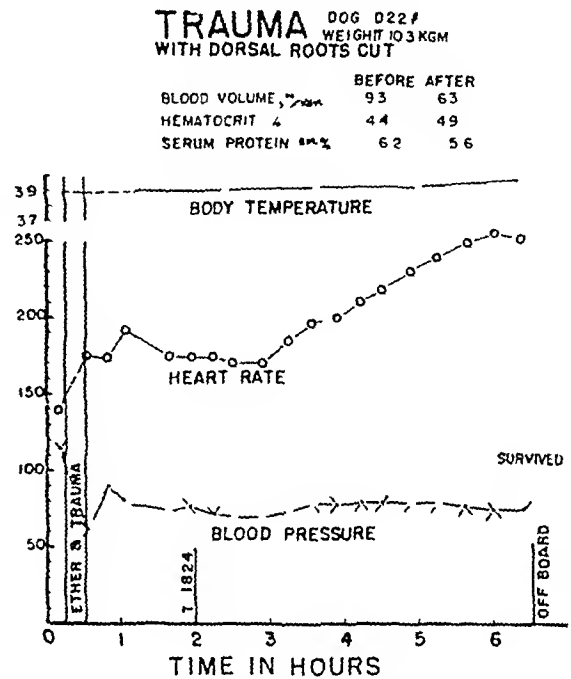


FIG 4—The clinical manifestations of a chronically deafferented dog (D 22) which has been subjected to muscle trauma. The blood volume reduction is comparable with that in dog H 13 and dog T 31 (Fig 1). Note the slowly increasing tachycardia and low blood pressure level in this dog and compare it with that in the hemorrhaged dog H 13. Like dog H 13, D 22 survived the injury (from Wang⁴⁴).

While the increased hematocrit in the trauma series and in the hemorrhage plus stimulation series (compared with that in the deafferent series and the simple hemorrhage series respectively) may be a liability, it is not of sufficient magnitude to alter the viscosity to such an extent as to be a factor responsible for the increased mortality rate in the former two series.⁴⁶

this more intense constriction develops much earlier in the clinical course than that associated with simple hemorrhage, a reduced volume flow over a relatively long period of time is the result. And although the early vasoconstriction of traumatic shock results initially in a higher blood pressure, its insidious action in contributing to prolonged tissue anoxia cannot be ignored^{46, 47}. While certain aspects of this concept are not new,⁴⁸ emphasis should perhaps be placed upon the early development of an intense constriction associated with trauma and its maintenance throughout the clinical course. Likewise, one might point out that adequate restoration of blood volume, undertaken sufficiently early before irreparable anoxic damage has occurred, should lead to recovery. Thus, although afferent impulses might appear to be of secondary importance to the reduction of blood volume, they nevertheless contribute deleteriously to the course of many traumatized animals and, indeed, in sublethal hemorrhages may well be the final precipitating cause of fatal shock.

It would be unwise to assume that a factor which is of predominant importance in contributing to the fatal course in one type of traumatic shock is necessarily of equal importance in shock produced by other traumatic means. For instance, in shock caused by tourniquet or crush, the increased apparent viscosity factor due to increased hematocrit values must also play a very important role in contributing to failure of blood flow^{42, 49, 50}. In burn shock there is, in addition, a toxic factor⁵¹. Human traumatic shock usually involves some external hemorrhage and the complication of bone fractures. On the other hand, hemorrhagic shock always involves some degree of trauma or pathology leading to the loss of blood. Furthermore, in many reported cases of shock in the human, the necessity of early therapy complicates the analysis of the relative importance of the contributing factors as well as the mortality rate. Richards and his colleagues^{52, 53} have, however, presented a series of well documented reports, comparing the pathologic physiology of various types of shock in man, in which measurements were carried out previous to any therapeutic intervention. In a Harvey Lecture,⁵³ Richards reported that arterial blood pressure tended to be less depressed in hemorrhage, and calculated peripheral resistance therefore higher (as compared with skeletal trauma). This is in contradiction to what we have observed in the canine experiments^{14, 15}. This difference could be conveniently ascribed to differences in the neuro-circulatory mechanisms of man and dog. However, Richards and his collaborators⁵⁴ have more recently collected 26 cases of skeletal trauma in shock and nine cases of external hemorrhage in shock. The average total blood volume values per square meter of body surface area in both groups were about the same, 1910 cc for the trauma cases and 1997 cc for the hemorrhage cases. For the former group, the systolic blood pressure was 76 mm Hg, diastolic 40 mm Hg and cardiac index 2.16 liters per min per square meter, for the latter group, systolic 76, diastolic 43 and cardiac index 2.42. Therefore, the hemorrhage group has a slightly lower calculated peripheral resistance than the trauma group, but the difference is not significant. Richards⁵⁴ gives the explanation for the relatively high blood pressure in the hemorrhage series.

reported in his Harvey Lecture,⁵³ that the gastro-intestinal and external hemorrhage subgroups were lumped together, and several of the gastro-intestinal cases were slow or chronic bleeders and had in part compensated for their blood loss. Whatever the explanation, it is important to stress the fact that one rarely encounters a clear-cut hemorrhage or trauma case in a patient as one does in experimental animals.

In any case, the fact that patients are frequently in shock following traumatic injury with little loss of blood continues to be the experience of many surgeons. And it is certainly true that painful stimuli in the human also give rise to an immediate pressor response.⁵⁵ There is, therefore, some basis for inferring that similar differences exist between hemorrhagic and traumatic shock in man and that, if such differences exist, they are of similar etiologic origin to those described here in the dog.

It is well, perhaps, to point out that our data are not to be interpreted as illustrating or accounting for *all* of the differences in causative mechanisms between traumatic and hemorrhagic shock. Indeed, afferent impulses appear to explain only in part the differences in mortality rate as well as the dissimilarities in clinical manifestations of these two groups of animals. For example, although the mortality rate of hemorrhaged dogs is increased by the addition of sciatic nerve stimulation, it does not attain the level of the traumatized group. Similarly, the deafferent animals withstand muscle trauma with a greater blood volume reduction than normal dogs undergoing the same procedure, but again do not survive an equivalent volume reduction as do animals following uncomplicated hemorrhage. Such quantitative observations indicate that perhaps still another factor or factors contribute to death in traumatic shock. The other most prevalent one in the literature is a toxic factor, although experiments designed to prove the existence of this component are difficult to interpret and the evidence thus far accumulated is not conclusive.

Recently, Aub, *et al*^{56, 57, 58, 59, 60} reported that ischemic muscle is an excellent medium for toxin production by *Clostridium welchii* which is normally found in dog muscle and skin. They further reported that the injection of fluid collected from such muscle, especially when artificially reinforced with exogenous clostridial toxin, resulted in a shock state similar to that of traumatized animals with the salient exception that the injected dogs showed an intense hemolysis. Aub, *et al*⁵⁸ showed, however, that animals suffering from ischemic muscle damage with subsequent exudation and reabsorption of the exudates were able to withstand graded hemorrhage to an equal total loss of vascular fluid as normal dogs. They concluded, therefore, that the experiments failed to demonstrate the presence in the general circulation of any noxious substance liberated from the ischemic muscle which accentuates the appearance of shock.

We could not, of course, rule out the clostridial toxigenic factor in our experiments. However, the short survival time (average 4 hours, range 2 to 6+ hours) and the presence of but slight hemolysis which was incident to the traumatic procedures are observations which are at variance with those found following the injection of exotoxin. In order to ascertain the importance of the

role of the clostridial toxic factor it would be necessary to study the protective action of polyvalent gas gangrene antitoxin, and to compare the mortality rate and clinical manifestations of treated traumatized animals with those of traumatized controls

However, in evaluating the afferent nervous factor in our experiments, the fact that the deafferentation conferred upon these animals the ability to withstand muscle trauma with a greater loss of blood volume than normal traumatized dogs—in neither groups were possible bacterial contaminants excluded—indicates clearly the importance of a neurogenic component in experimental traumatic shock

SUMMARIES AND CONCLUSIONS

1 Quantitative studies are presented which reveal a statistically significant difference in mortality rate between groups of hemorrhaged dogs on the one hand and traumatized dogs with equal blood volume reductions on the other. This indicates that loss of circulating volume alone is not adequate to explain the high mortality rate in experimental traumatic shock

2 Certain other differences in the clinical manifestations were observed in the two groups of animals, indicating an earlier and more intense activity of the sympathetic nervous system in the traumatized group

3 Animals subjected to sublethal hemorrhage followed by prolonged stimulation of the central ends of the cut sciatic nerves showed a mortality rate significantly higher than that of animals with an equal blood volume reduction from hemorrhage alone. The clinical signs exhibited by this group were closely similar to those shown in the trauma series

4 In another series of animals in which trauma was prolonged after previous deafferentation of the hind limbs, the mortality rate at a given level of blood volume reduction was significantly reduced from that shown by normal traumatized dogs. The clinical signs exhibited by this group were closely similar to those shown by the hemorrhaged animals

5 These studies indicate that an afferent nervous factor, second in importance to blood loss, is an essential causative mechanism in experimental traumatic shock

6 From numerous differences in clinical manifestations between the hemorrhage and deafferent-trauma groups on the one hand and the trauma and sublethal hemorrhage plus sciatic stimulation groups on the other, it is postulated that afferent impulses arising in the area of injury reflexly produce an intense and prolonged activity of the sympathetic nervous system. While such sympathetic activity operates to maintain a higher blood pressure level and may indeed be considered a compensatory mechanism early in the shock syndrome, the extreme and lasting vasoconstriction may become finally detrimental to the animal through further reduction in tissue blood flow and its sequelae—tissue hypoxia and acidosis

7 The relation of these experimental observations to the traumatic shock syndrome in man is reviewed

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A DISCUSSION OF TENDON REPAIR

WITH CLINICAL AND EXPERIMENTAL DATA ON THE
USE OF GELATIN SPONGE*

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THE REPAIR OF TENDONS in the hand calls for a variety of surgical technics. The problem is quite different in the finger, in the palm, in the wrist and on the back of the hand. The poorest results are in the ensheathed portion of flexor tendons. These cases frequently end up with an amputation. Although an amputation of a finger with a damaged flexor tendon is often desirable in a manual laborer, it may mean the loss of ability to earn his living in a skilled workman and where there are multiple injuries, repair may be imperative.

The causes of failure in the repair of ensheathed tendons are inherent in the structure of the tendon itself. This highly specialized physiologic unit is essentially an untwisted cable of fibro collagenous material covered by a single layer of easily damaged flattened cells. It glides in a tube-like sheath of similar material which is alternately thinned out over the joints and thickened along the shafts of the bones. The blood supply to an ensheathed tendon as commonly described consists of vessels carried in the vinculae (which constitutes a meso tendon) and of a central vessel in the tendon. After examining microscopic cross sections of at least 20 damaged tendons, I have been unable to identify the central vessel in any of them and I am convinced that this vessel is missing or becomes thrombosed following an injury.

When a tendon is severed the ends retract and considerable additional trauma is inflicted before the ends are recovered and reunited by suture. Experimental evidence¹ has shown that a tendon in healing first becomes a part of the surrounding tissues and later as the result of stimulus to function develops a new gliding mechanism. Unfortunately, it often happens that the traumatized tendon swells and becomes ischemically strangled in the tightly fitting sheath, and finally heals with dense adhesions to the sheath. Many of these adhesions were formerly blamed on infection but elimination of infection has not brought success in repairs although its presence certainly is disastrous.

Some adhesions may be present in certain locations without entirely limiting function. For example, a repaired profundus tendon may be partially adherent in the middle segment of the finger and still activate the end phalanx satisfactorily. This is because the tendon needs only a short gliding action here to mobilize its phalanx. The poorest results in tendon repair are obtained when the junction is made over the metacarpal heads and at the base of the fingers. Any limitation of glide here interferes seriously with finger action. There is no angle of pull to free the tendon here and the tendon distal to the repair also becomes adherent, thus a stiff finger is the usual result.

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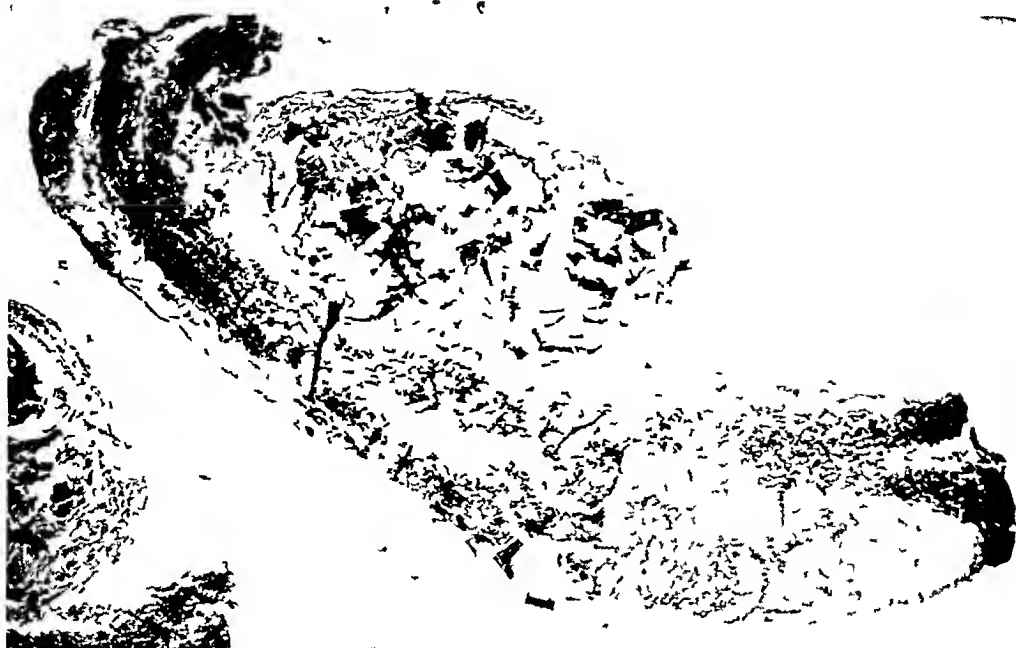


FIG 1—Low power photomicrograph of biopsy at two weeks Black material gelatin sponge



FIG 2—High power photomicrograph of biopsy at two weeks



FIG 3—Biopsy at one month showing no reaction about tendon Sponge absorbed



FIG 4—End-to-end suture showing extensive fibrosis

The principles underlying the repair of tendons have, as their basis the attempt to avoid adhesions in the dangerous areas. In the palm, tendons may be sutured and the repair protected from adhesions by using lumbricales muscles. At the distal phalanx no motion is necessary, hence suture in this location is usually successful. In an attempt to avoid suture in the unsuccessful locations, various authorities have advocated removing the damaged tendon and replacing it with a graft which is sutured in place in the palm and at the distal phalanx. Mayer² and Thatcher³ first insert a tube or rod to form a new tendon sheath later drawing the graft through this new channel. Bunnell⁴ prefers to graft in



FIG 5—Dog at two weeks showing sheath slit—no reaction about tendon

a complete unit of tendon and tendon sheath such as the palmaris longus with its paratenon. Unquestionably these methods have much to recommend them and there are many situations where they provide the only possible method of repair. The principal objection to the use of grafts in ensheathed tendon repairs is that the graft is poorly nourished at first and must depend on the surrounding tissues for its blood supply.

The trend in recent years has thus been more or less away from primary repairs of ensheathed tendons. Iselin,⁵ Dudley,⁶ Handfield Jones,⁷ Thatcher and other surgeons experienced in this field have definitely given up primary suture. On the other hand Bunnell and Koch⁸ and Mason⁹ still prefer primary repair but set a time limit on the interval between laceration and repair. Cer-

tainly infection in any case is disastrous. The author's experience is that an empty tendon sheath may get infected with results as damaging as a filled one. The trauma of the operative repair simply complicates this infection and makes it worse. Rarely, a primary repair is successful enabling function to be restored earlier, more completely and much more simply.

When a primary repair is undertaken, some additional procedure is usually done to prevent adhesions from completely limiting tendon motion. Bunnell recommends slitting the tendon sheath in the segment involved. Koch and Mason excise a window in the sheath over the repair site. In either primary or



FIG 6—Dog at one month. Tendon free.

secondary repairs, fat or fascia have been wrapped about the tendon junction and a variety of foreign substance such as amniotic membrane, cellophane, tantalum, foil, etc., have been tried to prevent the healing tendon from becoming adherent. Under any circumstances a good tendon is essential if a successful repair is to be effected. A scarred tendon lying in a scar tissue bed will inevitably become adherent. The success or failure of any foreign material introduced would certainly seem to depend on the ability of the body to convert this material into tendon sheath-like tissue.

One simple method of tendon repair which avoids the difficulties of either graft or end-to-end suture is the so-called tendon advance operation described by Cutler,¹⁰ and referred to by Littler¹¹ but otherwise rarely mentioned in the literature. In this procedure the proximal tendon stump is brought down and

sutured to the distal stump as close to its insertion as possible, excising the distal tendon between the point of laceration and the distal digital crease. This maneuver places the tendon juncture at the distal crease where no motion is needed and avoids the laceration area where adhesions are sure to form.

I have used this method successfully on about 15 cases since 1944. Practically, this procedure is most useful when the profundus tendon is severed in the middle segment of the finger. Theoretically, it might also be used to give

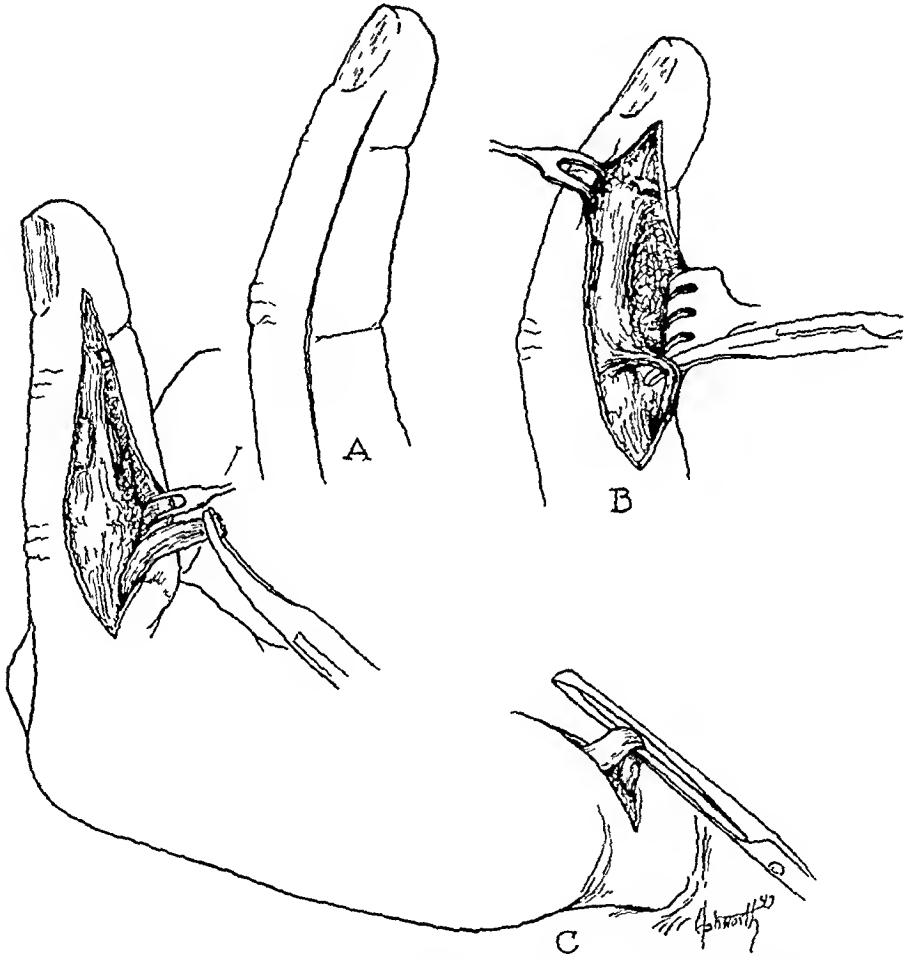


FIG 7—Technic of tendon advance operation. A Midlateral incision. B Dissection of scar tissue. C Tendon freed.

motion to the middle joint when the profundus is severed within an inch of the middle crease, since the tendon can usually be advanced about an inch. In practice a graft is usually used in this area.

In doing secondary repairs, the following technic is used (See illustration). The finger is opened through a mid lateral incision and the tendon sheath detached from the bony phalanx along one side. All scar tissue is excised and the tendon ends dissected out so that good tissue is available for repair. If the proximal tendon stump can then be drawn down to the distal digital crease with the wrist and finger flexed, the advancement operation can be carried out with

TENDON REPAIR

success. A considerable tension is present in some of these cases the tendon is secured by wire passed through a drill hole in the phalanx. A heavier wire than is usually described is used for this anchoring suture and it is inserted in such a way that it can be removed from the distal end. This allows the wire to be left in place a month if necessary without forming adhesions or causing infection. Before closing the incision, the exposed tendon is surrounded with strips of gelatin sponge.*

The wound is closed with external sutures only, leaving the remaining tendon sheath slit throughout its length. The hand is dressed in a plaster

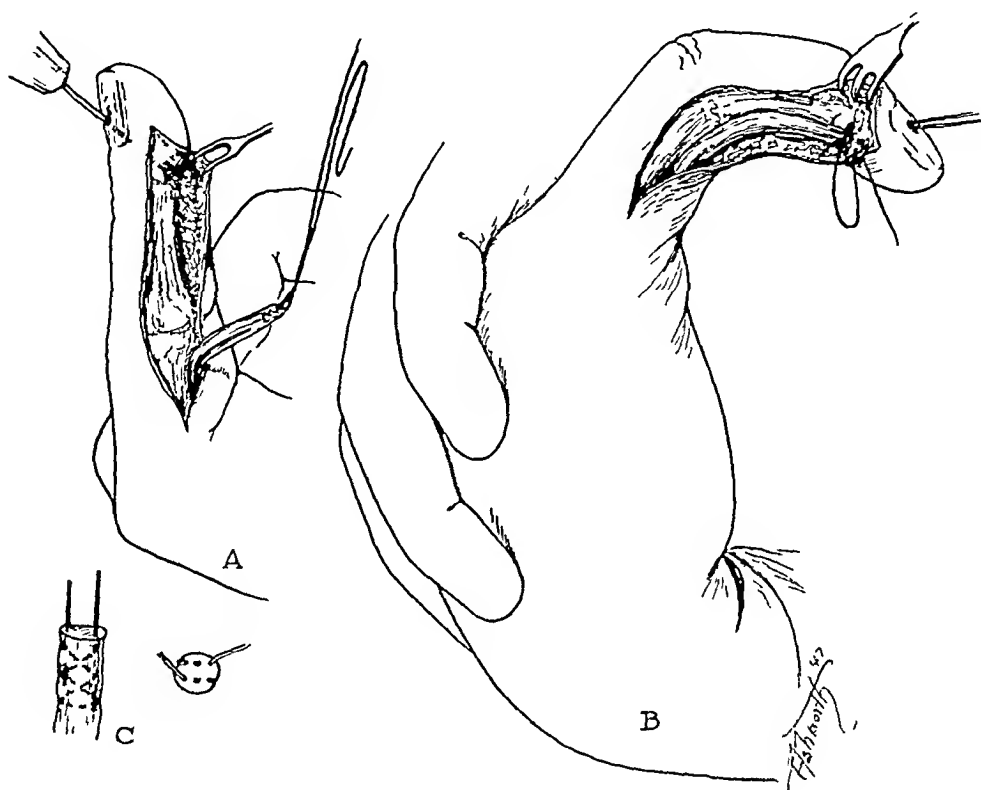


FIG 8 - Technique of tendon advance operation. A Suture inserted. Phalanx drilled. B Tendon advanced to new insertion. C Method of inserting suture.

mould with the wrist flexed. Active exercises are started after the skin wound heals, the patient being first instructed to attempt to gently, actively, straighten the finger.

The gelatin sponge was first used to control hemorrhage from the bare area left after excision of the scar. Later, it was found that these fingers had a better range of motion than was expected. To substantiate this clinical finding the following animal experiments were carried out. Six healthy dogs were used and the achilles tendon was exposed, wrapped with gelatin sponge and biopsied at two week intervals. The tendon was also sectioned, sutured and the juncture wrapped. It is fully realized that the achilles tendon is not an ensheathed tendon but it is the tendon which has been customarily used in

* Gelatin sponge used was Upjohn Co Gelfoam No 12

animal experiments From the accompanying photographs and photomicrographs, it can be seen that the gelatin sponge gross dissection does tend to show a shiny surface upon which the tendon glides Microscopically, there is very little reaction and there is found between it and the moving tendon a thin space lined by a single layer of flattened cells, very much like tendon lining When placed around a sutured tendon, however, dense adhesions are found

Clinically, it has been found that there are certain definite indications and contraindications to the use of this substance in tendon surgery It does definitely cause an increase in serum collections and autolysis of inadequately nourished tissues For this reason it should not be used about grafts or about tendon junctures as it prevents healing in these cases On the other hand it has been found useful in preventing sound tendons from becoming encased in adhesions in the tendon advance procedures

The following case reports indicate some of the cases in which gelatin sponge has been used and the results obtained There is also included a comparison series of the standard type case treated with and without gelatin sponge

CASE REPORTS

Case 1—WA Age 26 Caught thumb in rip saw 10/2/47 lacerating palmer surface, severing digital nerve and tendon Unsuccessful primary tendon suture done elsewhere Unable to move distal joint Repair 3/17/48 using author's technic with gelatin sponge Healed with serum collection Examination 6/23/47 almost full function present (See Fig 10)

Case 2—JC Age 59 Bottling machine broke bottle, lacerating ring and little fingers 2/11/47, severing digital nerves and profundus tendon of little finger Repaired 4/19/47 Author's technic with gelatin sponge wrapping Primary healing Examination 8/6/47, able to touch palm actively and forcefully Lacks a few degrees of full extension (Little finger usually least successful in tendon repairs)

Case 3—HM Age 26 Caught index finger on cylinder block 5/23/47 Lacerated profundus tendon and digital nerve Repair 7/14/47 Author's technic, gelatin sponge used Healed by first intention Examination 10/7/47 showed 45 degrees of independent active motion of distal joint Able to touch palm but 30 degrees lack of extension due to previous scarring

Case 4—CS Age 41 Saw laceration of right middle finger severing profundus tendon near insertion 8/16/47 Primary repair done elsewhere, unsuccessful Operation 1/5/48 found profundus tendon retracted into palm and degenerated Sublimis tendon adherent and inflamed Profundus excised, sublimis wrapped with gelatin sponge after freeing, distal joint fixed in 30 degree flexion Patient regained good painless range of motion, touches palm

Comment In some cases recovery of profundus is impossible To use a graft would necessitate sacrifice of good sublimis This is not advisable

Case 5—EG Age 30 Index finger cut in middle segment on tin strip 7/3/47 Digital nerve and profundus tendon severed Immediate repair Author's technic without gelatin sponge Examination 11/14/47 Has full extension almost full flexion (See Fig 11)

Case 6—BD Age 41 Finger cut by metal on drill press 6/20/46, both tendons severed in proximal segment Immediate suture done elsewhere through anterior incision Absolutely unsuccessful Repair 10/16/46, author's technic but without gelatin sponge Primary healing Examination 2/24/47 active motion 90 degrees proximal joint, 80 degrees middle joint, 30 degrees distal joint Finger tip almost touches palm

Comment—Enough of profundus left to carry out repair

TENDON REPAIR

Case 7—CR Age 32 Cut index finger on knife 6/46, both tendons cut in proximal segment Primary suture done elsewhere through anterior incision Absolutely unsuccessful Repair 1/27/47, author's technic without gelatin sponge Healed per primum Examination 4/29/48, tip almost touches palm

Case 8—PS Age 43 Plow shear fell onto hand 4/4/46 Suffered laceration middle and ring fingers across middle creases Profundus tendons cut both fingers Repair 6/25/46 Proximal tendon ends were resutured to distal stumps using pull out wires tied over buttons on ends of fingers Ring finger failed to function Reason, distal stump left too long Resutured 8/2/46 using author's technic Examination 11/6/46, active full motion of proximal joints All middle joints 90 degrees Distal joints 35 degrees Touches palm strongly

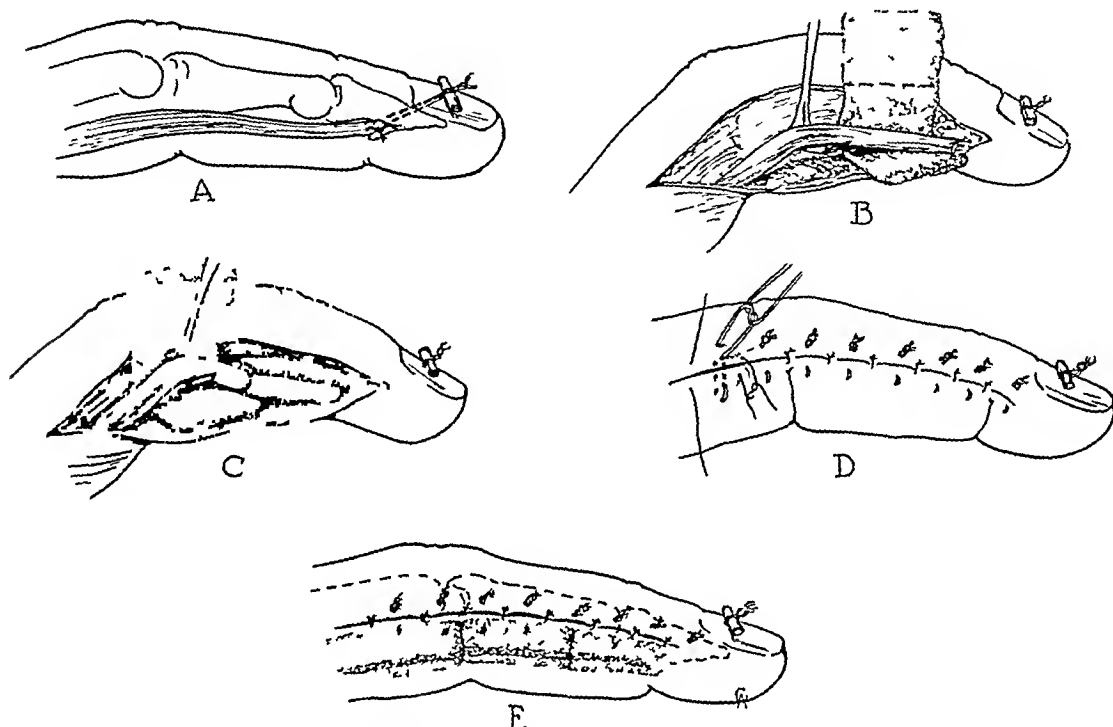


FIG 9—Technic of tendon advance operation A Tendon repair complete B and C Gelatin sponge wrapping applied D and E Wound closed

Comment—Fingertips scarred by buttons in this case Later cases drilling phalanx avoided this difficulty

TENDON GRAFTS

Case 9.—LP Age 20 Saw injury 2/14/47 sustaining amputations of little and ring fingers and part of thumb with loss of soft tissues over proximal segment of middle finger Soft tissue first replaced with abdominal flap Tendon graft inserted 6/21/47 surrounded with gelatin sponge Wound failed to heal Tendon removed 7/8/47, showed marked softening and inflammatory infiltrate Second tendon graft done without gelatin sponge 11/4/47 and was successful

Case 10—LS Age 37 Saw cut dorsum of hand 3/12/47, severed extensor pollicis longus Sutured elsewhere, function did not return Secondary repair was done 5/27/47 The extensor of the fourth toe was removed and used as a graft Tendon junctures were effected by interweaving tendon ends and these areas were wrapped with gelatin sponge Healing delayed Examination 7/1/47 showed some return of function but full extension was not present, evidently due to tendon junctures separating

Comment—Out of a series of tendon grafts done in the past few years, these cases are the poorest results of their respective types Gelatin sponge should not be used around tendon grafts

END-TO-END SUTURE

Case 11—CB Age 30 Glass cut volar surface of index finger 7/3/47 Both tendons cut at proximal crease Immediate repair using Bunnell suture at a distance technic Tendon juncture wrapped with gelatin sponge Healed kindly Examination 5 months later showed poor function (due to extensive adhesions at operative site) Case reoperated 4/10/48, tendon freed Good result

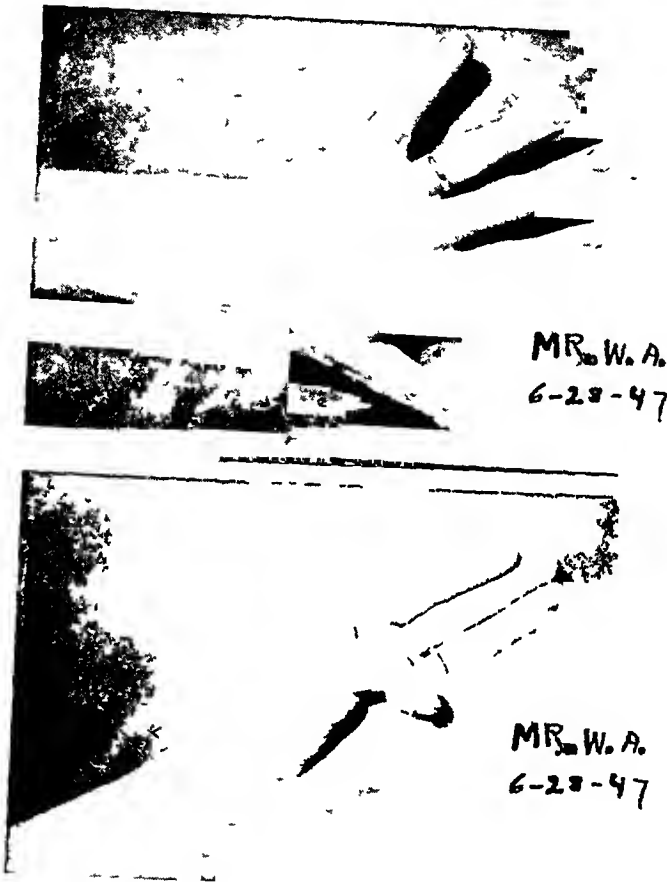


FIG 10—Illustration, Case 1 Flexor tendon repair in thumb showing full return of function

Comment—Animal experiment shows excessive fibrosis about tendon juncture See plate Gelatin sponge should not be used here

Case 12—NC Age 25 Run over by motor boat 8/4/47 Multiple lacerations of hand and forearm with fractures of carpals and metacarpals, and division in carpal canal of flexor pollicis longus and both flexors of index finger, also double lacerations of flexor carpi radialis in forearm Repair 8/25/47 Through boot hook incision, the transverse carpal ligament being detached on its ulnar side, the wrist and forearm were widely opened Tendons in canal repaired end to end using Bunnell stitch with stainless steel wire Tendon juncture wrapped with gelatin sponge to protect median nerve which had been superficially lacerated Tendon graft used to fill gap in forearm in flexor carpi radialis No gelatin sponge Wound healing satisfactory Examination 5/4/48, full function but thumb and index finger working together

TENDON REPAIR

Comment—Apparently gelatin sponge tolerated well in carpal canal I believe, however, that a sleeve of areolar tissue would have been better here

Case 13—DG Age 20 Window glass cut dorsum of wrist 6/14/47 Multiple laceration, all tendons being severed in center of posterior annular ligament Repaired 12 hours later Finger extensors repaired by interweaving their ends, extensor carpi ulnaris end to end using a pull out wire fastened over a button Gelatin sponge used about all tendon junctures Healed by first intention Examined 6/3/48, full function but extensive fibrosis about tendons

TENDONS CUT IN WRIST

Case 14—RH Age 16 Fell into water catching right wrist on bolt of submerged log 4/12/47 Multiple lacerations Flexor carpi radialis severed near insertion Immediate repair using pull out wire—fastened to button in palm Tendon juncture wrapped with gelatin sponge Healed kindly Full function in one month

Case 15—VO Age 22 Fell, cutting palm and snuff box area 5/4/47 Abductor pollicis longus sutured with pull out wire fastened to button on dorsum of thumb Tendon juncture wrapped with gelatin sponge Wound healed by first intention Examined one month later Full function

Case 16—JO Age 56 Stuck hand through glass door 7/30/47 Multiple lacerations severing flexor flexor carpi radialis, extensor pollicis brevis, abductor pollicis longus also ulnar nerve and flexor carpi ulnaris Tendons repaired with pull out wires tied over buttons in palm, junctures wrapped with gelatin sponge Wound healed per primam Examination 8/27/47 showed good return of function Photo 4/30/48, almost full function even of ulnar nerve Small finger muscles not working

Comment — Gelatin sponge apparently well tolerated on back of hand and wrist but not necessary

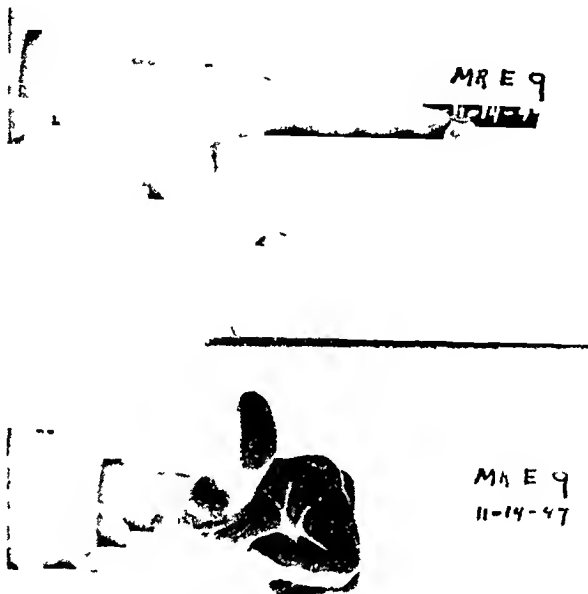


FIG 11—Illustration, Case 5 Index finger tendon severed in middle segment Showing amount of function four months later

DE QUERVAIN'S DISEASE

Case 17—MH Age 48 Suffered fractured navicular 7/28/48 Painful swelling along tendon sheath began two months after removal of cast Operation 1/8/47 Typical stenosing tenovaginitis of sheath, of extensor brevis and abductor longus of thumb Sheath split Patient was well for two months, then symptoms recurred Reoperated 4/4/47 Found tendons again markedly inflamed Excised sheath and granulating tissue, wrapped tendons with gelatin sponge Healed uneventfully Reported cured 12/20/47

Comment—Apparently gelatin sponge well tolerated in this case

DISCUSSION

The variety of cases presented above include not only ensheathed tendons but also tendons surrounded with paratenon, it being the author's purpose to

ting this material in every conceivable type of tendon repair. In analyzing the results obtained, it can be seen that in most locations there is no special advantage in using the gelatin sponge.

SUMMARY

Clinical and experimental data on the use of gelatin sponge is presented with the following conclusions:

1 The sponge may be placed around a sound tendon without danger and apparently allows earlier free tendon motion here.

2 When used about a tendon juncture the sponge causes excessive fibrosis and prolonged fixation of the tendon.

3 Tendon grafts are apparently autolyzed when surrounded by gelatin sponge.

Experimental work was carried out at the University of Oregon Medical School laboratory.

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A TECHNIC OF EXPOSURE FOR DIVERTICULA OF THE THIRD AND FOURTH PARTS OF THE DUODENUM*

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The technics of exposure utilized in the operative treatment of diverticula of the third and fourth parts of the duodenum have apparently changed little since the publication of the classic case reports of Forssell and Key (1915), Basch (1917) and Maclean (1927). Access to the duodenum has ordinarily been sought through the transverse mesocolon or through the gastro-colic omentum and the lesser omental sac. Diverticula occurring in anterior locations have then generally been dealt with by simple dissection, but procedures which have led to duodenal mobilization or elevation of the pancreas have almost invariably been used in the search for diverticula not at once exposed to view.

The mobilization of the duodenum in the latter instances has been achieved by recourse to a method commonly attributed to Kocher. Here the duodenal segments are reflected medially and thus restored to the position in which they lie before rotation during embryonic life. Additional technics of mobilization which have also been suggested are not known to have been used in the treatment of these lesions. A medial approach had been proposed by Clairmont and Schinz (1920), but in the review by Morton (1940) this procedure was considered difficult and ill-advised. A method used by Vautrin and Fourche (1923) for other lesions in the region of the proximal duodenum was thought suitable for diverticula of the distal segments by Kellogg and Kellogg (1931). A portion of the transverse colon was turned down in this procedure, and the duodenum was reflected with the pancreas medially. Subsequent reference to these methods has been limited because the surgical treatment of diverticula has not often been advised.

We wish to call attention at this time to a technic of duodenal mobilization which we have not found emphasized in any previous report.

TECHNIC

The duodenum is exposed by turning the transverse colon, mesocolon and great omentum upwards. An incision is begun in the posterior layer of the parietal peritoneum, just below and parallel to the inferior duodenal edge, and from this point it is extended, medially and laterally, until it underlies the third and fourth parts of the duodenum. The superior mesenteric vessels are retracted towards the patient's right, and by means of sharp dissection which

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FIG 1--Roentgenographic appearance of the diverticulum 6 weeks prior to operation

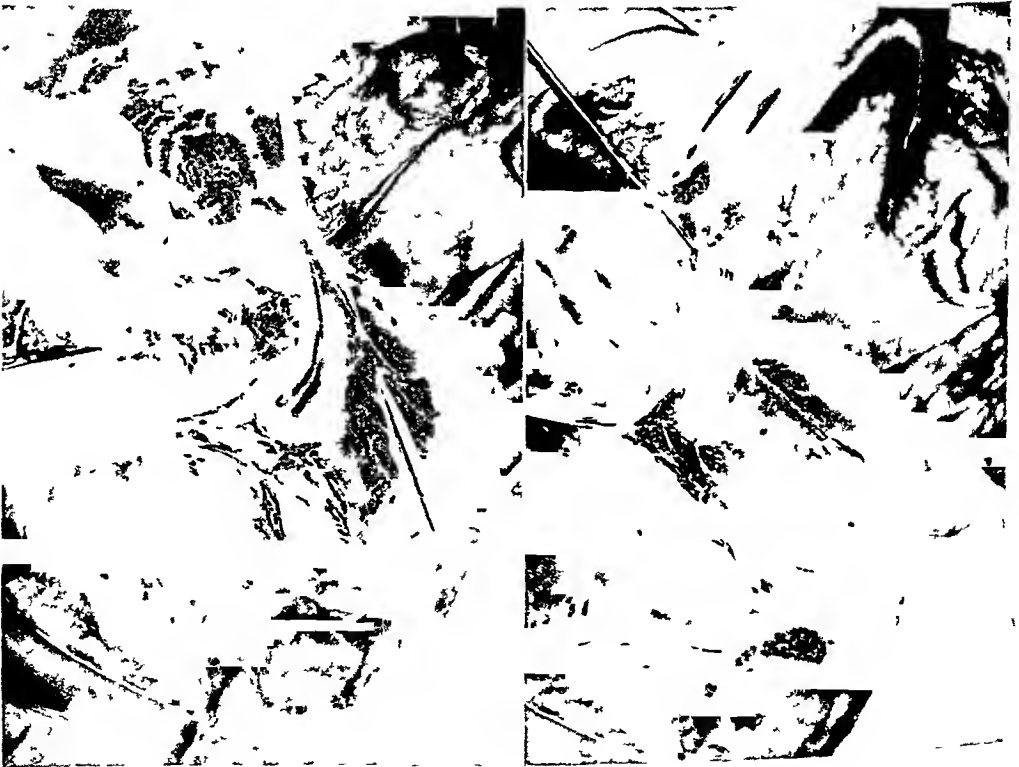


FIG 2

FIG 3

FIGS 2 and 3—Photographs of a dissection of a cadaver to illustrate the mobilization of the third and fourth parts of the duodenum. Fig 2 shows the exposed duodenal segments *in situ*, and Fig 3 the segments after their dissection from the duodenal bed and after their rotation towards the subject's right.

is advanced proximally the outlined duodenal segments are separated from their bed. Their reflection also towards the right, which sometimes requires division of the ligament of Treitz, then brings their posterior surfaces into satisfactory view and permits easy access to the diverticula in this region.

This technic has been of value in a recent operation where massive fat deposits greatly interfered with the exposure of the pancreas and duodenum. Little bleeding was encountered, and the ease of the procedure was thought worthy of comment. The diverticulum (Fig 1) originated from the mid posterior surface of the third part of the duodenum and lay wedged between the pancreas and the duodenal wall. Bulbous in outline, it was about 2 inches long and about 3 inches wide, with a neck $1\frac{1}{2}$ inches across. Dissection of the diverticulum from its pancreatic bed was accomplished easily. Amputation at the base was performed between two clamps, and closure of the defect in the duodenal wall was achieved by transverse suture and infolding of the stump. An adequate exposure was afforded for each stage of this procedure.

The effectiveness of this approach has also been demonstrated upon the cadaver (Figs 2 and 3). With its application we believe that diverticula of the third and fourth parts of the duodenum may be identified without recourse to such auxiliary measures as the air injection technics suggested by Walzel (1935) and by Mahorner and Kisner (1947). We are also of the opinion that extensive elevation of the pancreas will not frequently be needed.

SUMMARY

An account is given of a technic of duodenal mobilization which has been found of value in the exposure of diverticula of the third and fourth parts of the duodenum.

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THE SURGICAL TREATMENT OF HERNIA IN THE AGED

A STUDY OF EIGHTY-TWO CONSECUTIVE PATIENTS
OVER SIXTY YEARS OF AGE*

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THIS PAPER IS PRESENTED not merely as a statistical study but as a plea for the surgical treatment of hernia in old people. Many elderly patients complain for years of pain in the area of the abdomen affected by the hernia, or struggle with a truss prescribed by some well-intentioned physician, until incarceration, strangulation or intercurrent disease settles the issue. It has been assumed too often that a sedentary life or a degenerative disease precludes the necessity for herniorrhaphy. Yet the persistent symptoms of hernia themselves contribute largely to a state of invalidism. The teaching expressed in standard text-books of Surgery is exemplified in the "Textbook of General Surgery," by W H Cole and R Elman,¹ who state in their chapter on Inguinal Hernia—"In elderly people the question of operability presents itself. If the patient is no longer required to work, and the presence of a hernia produces only moderate symptoms, there may be no advantage in performing an operative repair."

Dulin,⁷ in his series of 263 cases of elective hernioplasty in the aged, had ten deaths, or a mortality of 3.8 per cent. He had an infection rate of 8 per cent in cases done under local anesthesia. He, therefore, concluded that the repair of inguinal hernia in old people was dangerous and unsatisfactory.

However, there are other authors who believe that old people can safely receive the benefits of surgical treatment. In 1940 Quigley² analyzed 100 consecutive cases of inguinal herniorrhaphy in patients over 65 years of age. One of his patients died of pulmonary embolism 23 days after operation, so that his operative mortality was 1 per cent, certainly not a prohibitive figure. Both Brooks³ and Clagett⁴ feel that it is no longer logical to accept old age as an excuse for withholding operative treatment for dangerous and disabling diseases. With the gradual change in our population and the increase in the proportionate number of elderly patients³ the treatment of this group of people will demand more and more of the surgeon's attention. Both Bailey⁵ and Morton⁶ believe there is little evidence for the truth of the popular opinion that advanced age is a strong contraindication for operative treatment.

GENERAL CONSIDERATIONS

Between April, 1939, and April, 1946, 82 patients over 60 years of age were admitted to the second surgical division, for the treatment of various types of hernia. Practically all came from the City Home for the Aged and from the medical wards. Twenty of these were emergency cases. There were 70 males

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and 12 females. Ninety-five operations were performed on these 82 patients, 78 for inguinal hernia, 10 for femoral hernia, three for umbilical hernia and four for ventral hernia. Of the group of 20 emergency cases (incarceration and strangulation), nine were inguinal hernia, seven femoral, two ventral and two umbilical. In the group of elective cases there were 12 operations for direct, 52 for indirect, six for sliding and eight for recurrent inguinal hernias.

Thirty-six patients were between 60 and 70 years of age, 35 were between 70 and 80 years, 10 were between 80 and 90 years, and one woman with an incarcerated femoral hernia was 102 years old.

Fifty-seven patients or 69 per cent of the total number had a complicating chronic or degenerative disease. Thirteen had generalized arteriosclerosis, 12 had hypertension, seven coronary artery disease, four diabetes, and the others are listed in Table II.

TABLE I—Operations for Hernia

1	Total number	95
2	Inguinal	78
	(a) Indirect	52
	(b) Direct	12
	(c) Recurrent	8
	(d) Sliding	6
3	Femoral	10
	(a) Male	2
	(b) Female	8
4	Umbilical	3
	(a) Male	2
	(b) Female	1
5	Ventral	4
	(a) Male	1
	(b) Female	3

SYMPTOMS

The predominant symptom among the 62 patients in the elective group was pain, usually localized in the region of the hernia. The pain was almost constant and was aggravated by walking and standing. Thirty-eight patients presented this complaint. Eight patients complained only of the mechanical inconvenience of a protruding mass. A history of incarceration was given by three. Another three patients complained of pain and protrusion, and ten had no discomfort from their hernias. In short, 52 out of 62 old people who came under our observation had persistent discomfort or pain.

Seventeen patients had had their trouble for more than 10 years, two between five and 10 years, and 18 less than five years, while in 25 cases the length of time was not given in the history. Incidentally, seven gave a history of having worn trusses, and all seven maintained that the trusses either failed to retain the mass or else caused increased pain.

TECHNICAL CONSIDERATIONS

The 95 operations in this series were performed by 10 visiting surgeons and 14 resident surgeons. Forty-one of the procedures were done under local block anesthesia with either 1 or 2 per cent novocaine. General anesthesia,

usually inhalation of cyclopropane, oxygen and ether, was used for 30. Spinal anesthesia was the method employed in 15 cases. A combination of local infiltration and general inhalation narcosis was used in three patients while six operations were performed under combined local infiltration with intravenously administered pentothal. The method of choice was local block anesthesia with 1 per cent novocaine. In instances of mass replacement of bowel from scrotum into peritoneal cavity additional inhalation or intravenous anesthesia was sometimes necessary.

TABLE II—*Associated Disease*

Disease	Number
1 Generalized arteriosclerosis	13
2 Coronary artery disease	7
3 Hypertension	12
4 Diabetes	4
5 Neurologic disease	
(a) Parkinson's	2
(b) C N S lues	2
(c) Tabes dorsalis	1
(d) Hemiplegia	1
(e) Glioblastoma multiforme	1
6 Pernicious anemia	2
7 Rheumatoid arthritis	3
8 Peptic ulcer	1
9 Hypertrophied prostate	4
10 Caisson disease of bone	1
11 Tuberculosis of chest wall	1
12 Cataract	1
13 Cirrhosis	1
Total	57

Standard methods of repair were used. In inguinal hernia the Halsted technic was used in 42 cases, the Bassini in 28, the Ferguson in one, and orchidectomy with repair in seven. In femoral hernia the femoral canal was closed by external suture in eight cases and in two instances an abdominal exploration was also necessary. Three umbilical hernias were repaired by transverse overlap and the four ventral hernias by vertical overlap.

Silk was used as the suture material in 65 cases and catgut in 30.

COMPLICATIONS OF OPERATION

Infection of the operative wound occurred in five cases, giving an infection rate of 5.2 per cent. Only one of these infections involved structures below the level of skin, the organisms cultured from the wound being *staphylococcus albus* and *bacillus coli*. This moderately severe infection took place in a case done under general inhalation anesthesia for strangulated inguinal hernia with resection of bowel. In the other four cases the infection was limited to the skin. Two of the latter were done under local anesthesia and the remaining two under spinal anesthesia. Response to the sulfonamides and penicillin was prompt.

Bronchopneumonia complicated the postoperative course in 13 cases. Treat-

ment with sultadiazine and penicillin was usually effective. Pneumonia will again be discussed in a subsequent paragraph as a cause of death.

Two patients developed a posterior claval phlebitis which responded quickly to treatment without sequelae. There was no instance of pulmonary embolus.

One patient had a cerebral accident on the 16th postoperative day. Another had a complicating epididymitis following operation. One man with cirrhosis of the liver, transferred from the medical ward for the emergency treatment of an umbilical hernia, suffered a massive gastro-intestinal hemorrhage postoperatively. Finally, one 83-year-old female, operated upon for a huge strangulated umbilical hernia, went into shock from which she did not recover.

MORTALITY

Of the 62 patients who were operated upon as elective cases, one died, giving us a mortality rate in elective surgery of 1.6 per cent. When operation became emergent, as happened in 20 patients, the figure rose sharply to eight deaths—a mortality of 40 per cent. In the entire series of 82 patients, there was a total of nine deaths, constituting a mortality of 10.9 per cent for elective and emergency cases. Following are brief outlines of the cases that died.

Case 1—*Elective*. S. B., male, age 66, operated upon for large right sliding inguinal hernia involving cecum, on July 16, 1943. Twelve days later smaller left inguinal hernia repaired. On 14th postoperative day, while out of bed, he had a right hemiplegia and died on the 16th postoperative day. Necropsy—glioblastoma multiforme of brain, pulmonary edema, small right perinephric abscess.

Remaining eight cases were all emergent.

Case 2—W. H., male, aged 74, in hospital for cirrhosis of liver and chronic myocarditis, was operated upon for strangulated umbilical hernia, and died on second postoperative day after vomiting a large amount of blood.

Case 3—E. B., female, aged 83, was operated upon for a huge strangulated umbilical hernia containing most of colon, ileum and part of jejunum. She died five hours postoperative of shock.

Case 4—E. B., female, aged 72, was operated upon for an incarcerated ventral hernia and died on the 4th postoperative day of pneumonia. Also had an old left hemiplegia, diabetes, auricular fibrillation.

Case 5—T. L., male, aged 78, in hospital for arteriosclerotic heart disease underwent operation for strangulated left inguinal hernia and died six weeks later of pneumonia.

Case 6—A. F., female, aged 60, operated upon for strangulated left femoral hernia and gangrene of small intestine, died on the second postoperative day in uremia.

Case 7—G. McE., male, aged 75, in hospital for pernicious anemia, was operated upon for strangulated right inguinal hernia and died two months later of sacral decubitus and pneumonia.

Case 8—V. B., female, aged 81, in hospital for diabetes and generalized arteriosclerosis was operated upon for incarcerated ventral hernia and died eight days later of cerebral accident and pneumonia.

Case 9—G. C., female, aged 80, in hospital for hypertension and chronic cardiovascular disease, died 14 days after operation for strangulated right femoral hernia, of pneumonia and uremia.

These summaries are presented not only to give a description of the causes of death in our series but also to give an insight into the type of patient treated. Six of these people were already in hospital for treatment of a chronic disease.

and developed their acute surgical condition while on the medical wards. In addition, since the Goldwater Memorial Hospital is an institution for the chronically ill, patients continue treatment on our wards longer than in the average general hospital. It will be noted that cases 1, 5, 7 and 9 died two weeks or longer following operation, when they were actually recovered from the immediate effects of surgery. They were still on our wards because of some chronic medical disease, and therefore were included in our surgical mortality figures.

COMMENT

The series of cases just described constituted a unique "poor-risk" group of patients. Most of them came from the New York City Home for the Aged on Welfare Island. They were people who, in general, had been subjected all their lives to the physical and psychic trauma of poverty. Others were transferred from the medical wards where they were being treated for chronic medical conditions.

Patients in the elective group were prepared for operation as for any major surgical procedure. Protein, vitamin and hemic deficiencies were corrected by diet and, when necessary, by parenteral therapy. Consultation with the medical service for the evaluation and correction of pulmonary and cardiac disease was of valuable aid. Thus, three of our patients required careful digitalization before operation. All three had uneventful postoperative courses. It was deemed inadvisable to operate upon patients who had kidney insufficiency as indicated by high nonprotein nitrogen content of the blood. Two men in the latter category underwent successful operation for hernia after preliminary surgery for hypertrophied prostates. Patients with active pulmonary disease were not subjected to surgery.

The anesthetic of choice is 1 per cent novocaine block infiltration, for inguinal, femoral and small umbilical hernia. When this is inadequate, supplementary inhalation of cyclopropane and oxygen can be used. In this series of cases, wound infection was not increased by the use of local anesthesia.

Silk is the favored suture material since its use, according to the principles of Halsted,⁸ produces less wound reaction than catgut. No particular technique of repair is recommended, since individual cases vary so much.

Of more importance than the type of repair is strict adherence to the fundamental surgical principles of gentleness in the treatment of tissues and avoidance of elaborate procedures. When the patient agrees, orchidectomy is justified if deemed absolutely necessary for the security of the repair. In bilateral inguinal hernia, we prefer that the operation be done in two stages at about a 12-day interval.

The patient is allowed out of bed on the day after operation. Here, again, the usual precautions in regards to early ambulation should be taken. Thus, a rapid pulse or high temperature indicates that the patient is to remain in bed.

Pneumonia was the most frequent complication. The 13 patients whose courses were complicated by pulmonary disease had the bronchopneumonic

type The disease became evident at any time from the second postoperative day onward, and the earliest physical signs were found at the bases of the lungs Of the nine patients who died, four had pneumonia as a cause of death

Infection of the operative wound was not a serious complication in this series of cases Only one severe infection, and four superficial ones occurred The repair remained intact in all five cases

The striking factor in our mortality figures was the greatly increased risk in emergency surgery for hernia Thus, there was one death in 62 patients who were treated as elective cases and eight deaths in 20 emergency cases It would seem to be logical medicine and good surgery to treat the elderly patient for hernia before he becomes a surgical emergency

The question of recurrence of hernia will not be considered in this paper

CONCLUSION

A series of 82 poor-risk patients over 60 years old, operated upon for hernia, has been presented Sixty-nine per cent of these patients had a complicating chronic or degenerative disease Fifty-two of the 62 patients in the elective group had persistent symptoms from hernia which contributed greatly to their invalidism Where trusses were worn, they were inadequate Operation had been deferred for years because of "old age" or a chronic medical condition

In the group of 62 elective cases, one patient died of a cerebral accident and brain tumor 16 days after operation Of 20 patients subjected to emergency surgery, 8 died The contrast between the mortality figures in these two groups offers a graphic argument for the elective use of surgery in the treatment of hernia in the aged

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SURGERY IN SITUS INVERSUS*

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TRANSPOSITION OF THE VISCERA is an unusual anomaly in which the positions of the abdominal and thoracic viscera are reversed, producing a relationship which has been well described as "the mirror image of normal". Although this condition is, in itself, not a serious hazard to normal health and longevity, its early recognition is of extreme importance in the treatment of many diseases, especially those requiring early surgical intervention. The purpose of this report is to present a brief review of the literature on this subject and to summarize those recorded cases in which surgery has been performed.

HISTORY

Although Aristotle¹¹⁷ first described this anomaly in animals, it was not recognized in the human until the 17th century when it was described in the writings of Fabricius¹³⁴ (1600), Servicius¹³⁴ (1615) and Riolan⁹² (1650). Beck⁷ states that one of the earliest recorded cases was that of Marie de Medici, Queen of France. Kuchenmeister¹¹⁷ in 1864 emphasized the importance of percussion and auscultation as an aid in diagnosis and Vehemeyer¹¹⁷ in 1897 was the first to discover a case by roentgen-ray examination. Since then cases have been recognized with increasing frequency, so that by 1938 Larson¹¹⁴ estimated that over 475 had been reported.

INCIDENCE

The incidence has not as yet been established definitely, varying from 0.02 to 1 per cent as recorded in the literature (Table I). The close relationship between the total incidence found at autopsy (1-6, 164) and that found in mass chest surveys (1-6, 581) suggests that this anomaly will probably be encountered at least once in every six to eight thousand individuals. Although a busy surgeon, therefore, may expect to encounter this anomaly only once or twice in a lifetime, it is his responsibility in order to protect these individuals and to avoid embarrassing errors to familiarize himself with this anomaly and to consider it as a remote possibility in all cases of obscure abdominal pain.

ETIOLOGY

The etiology is also obscure. Apparently the embryo of a few millimeters is symmetrical so that in a medial sagittal plane the right and left sides are the mirror image of each other. According to Sherk,¹¹⁷ there is an altered relationship between the embryo and chorion, in which the right side of the embryo, rather than the left, is nearer the blood supply. As a result the cardiac tube assumes the position of a reverse "S" rather than a normal "S". Virchow¹¹⁷ emphasizes the significance of the reversed spiral twist in the umbilical

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cord Von Baer¹³⁰ believes that the causative factor is an altered relationship between the embryo and the umbilical vesicle and Serre¹ suggests that an abnormal development of the omphalomesenteric artery and liver may also play a role

Because of the various degrees of transposition often seen in monsters, McMurrich³⁸ is of the opinion that these individuals are in reality the right twin of a duplicate monster, the left having been absorbed. Refutation of this theory lies in the fact that situs inversus is seldom seen in identical twins

TABLE I—Incidence

Clinical Examinations		
Lewald ⁷⁸	1	135,000 Army Recruits
	3	63 000 clinical exams
Hospital Admissions		
Massachusetts General Hospital ²	23	232 112
Willis ¹³³	3	10 000
Mayo Clinic	10	347 000
Prescott and Zollinger ¹⁰¹	3	15 374
X-Ray Examinations		
Lewald ⁷⁸	29	40 000
(Many of these were referred after diagnosis had been made)		
Francisco and Ongpin ⁴¹	36	126 000
Sier and Clenet ¹¹³	30	280 000
Prescott and Zollinger ¹⁰¹	1	1,072
	5	50 000
Total	101	503,930
Minus	29	40 000
	72	463 930
Ratio	1	6 587
Autopsies		
Bell ⁹	3	30 000
Mayo Clinic (personal communication)	3	10 000
Lewald ⁷⁸	1	50 000
Gunther ²	3	22 000
Adams and Churchill ⁹	1	8 000
Kehr ⁶⁹	2	10,000
Francisco ⁴¹	4	10 000
Rossler (Gall and Woolf) ⁴⁵	3	22 000
Total	20	117 000
Ratio	1	6 164

Some authors suggest that this is an acquired anomaly resulting from environmental influences on the fertilized ovum. Mall, Stockard and Newman² independently have emphasized the etiological importance of temperature, nutrition and growth rate. Speman⁹² has been able to produce various degrees of transposition in a few instances by surgically altering the medullary plate.

Other investigators believe this is an inherited anomaly arising in the germ plasma itself. Sumner and Heustis¹³⁴ conclude from studies on insects that situs inversus is the result of a recessive gene, probably in the third chromo-

some This view is supported by Cockayne's¹³⁴ study of a large number of families and also by Feldman's³⁷ report of three cases in one family, the parents of which were first cousins Reports by Feldman and Needle³⁸ and by Gall and Woolf⁴⁰ reveal that in the literature there are 25 instances of two or more cases in the same family, making a total of 54 recorded cases in which there is a known relationship Although the authors conclude that such instances are exceedingly rare, the fact that less than one thousand cases in all have been recorded suggests that at least 1 in 20 is apt to have a relative with the same anomaly, offering rather strong evidence that these individuals are really mutants

Adams and Churchill² suggest that there may be both the hereditary and the acquired types, the first giving rise to normal individuals and the latter to true monsters showing all gradations of transposition as well as other developmental anomalies

TABLE II—*Ages and Sex at Time of Surgery*

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	Not Given	Total
Number cases	8	30	29	17	11	8	3	36	144
Sex									
Males									48
Females									65
No information									31
Total									144

CASE MATERIAL

Although this review attempts to be exhaustive, some cases have undoubtedly been overlooked Also many of the records are brief so that all of the desired information is not present in each case A review of the available data however, summarizes fairly well past surgical experience with this anomaly and emphasizes the errors that have been made because the condition was not recognized

The available literature reveals records of 144 patients with situs inversus who were submitted to 158 surgical operations The transposition was complete involving all of the viscera in 125 cases, and partial, involving one or more but not all of the organs in 19 There were 48 males and 65 females The ages at the time of surgery varied from 10 days to 64 years, but over one-half were operated on in the second or third decade (Table II)

The 158 operative procedures are summarized in Table III There were 99 operations for appendicitis 24 for gallbladder disease, eight pelvic laparotomies five stomach operations, two nephropexies, nine thoracic operations, one repair of a rectovesical fistula and 11 operations for bowel obstruction (eight in the small bowel and three on the colon) Excluded from this study are one thyroid two perineal repairs, three hernioplasties) and one parotid resection Also excluded are those cases with visceral mal-rotation or those with visceral mal-position The time of diagnosis, placement of incision, and the location of pain

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TABLE III—*Operative Procedures*

I	Operations on the appendix (96 cases operated on)	99
	Appendectomy	77
	Drainage of appendical abscess	3
	Procedure not clear	5
	Exploration, appendix not found	14
II	Operations on the biliary tract	24
	Cholecystectomy	17
	Cholecystectomy removal of common duct stones	4
	Cholecystostomy removal of common duct stones	1
	Cholecystostomy	1
	Congenital absence of gallbladder, removal of common duct stones	1
III	Operations on the stomach	5
	Gastric resection for carcinoma	1
	Gastro enterostomy for carcinoma	1
	Closure of perforated duodenal ulcer	1
	Gastro enterostomy for gastric ulcer	1
	Gastric resection for gastric ulcer	1
IV	Nephropexy	2
V	Bowel obstruction	11
	Adhesive small bowel obstruction	2
	Congenital obstruction duodenal-jejunal junction	1
	Accessory spleens with partial small bowel obstruction	1
	Volvulus of the small bowel	1
	Ileostomies in case of ileocecal T B with bowel obstruction	3
	Resection of inflammatory tumor of sigmoid	1
	Exploration for congenital stenosis of sigmoid	1
	Diverticulitis sigmoid	1
VI	Pelvic laparotomies	8
	Uterine suspension etc	3
	Oophorectomy	2
	Ectopic pregnancy	1
	Hysterectomy	2
VII	Thoracic operations	9
	Lobectomy for bronchiectasis (4 patients)	6
	Multiple pneumothorax	1
	Pleuroscopy	1
	Removal of bullet	1
VIII	Rectovesicle fistula	1
	Total number of cases	144
	Total number operations	159
	(One case had a gastro enterostomy and cholecystectomy at same operation) Minus	1
	Total number of operations	158
	Other Extra-Cavity Operations not included in Review	
IX	Perineorrhaphy and colporrhaphy	2
X	Thyroidectomy	1
XI	Parotid tumor	1
XII	Hernioplasty	3

are summarized in Tables IV V and VI There is a discrepancy in the figures because one patient had both a cholecystectomy and gastroenterostomy performed at the same time and therefore is considered in both the gallbladder and stomach groups

APPENDICITIS

Appendectomy was performed in 77 cases, appendicial abscesses drained in three, and the abdomen closed without finding the appendix in 14 In three of the latter, the appendix was removed later by a second operation In five cases the operative procedure was not clearly stated The pathology as given

TABLE IV—*Time of Diagnosis*

Diseases of	Number Operation	No Data	Diagnosis Before Operation	Diagnosis During Operation	Diagnosis After Operation	Total	Operation Not Accomplished
Appendix	99	26	39	24	10	99	13
Gallbladder	24	1	16	6	1	24	0
Pelvic laparotomy	8	2	3	3	0	8	0
Stomach and duodenum	5	0	3	2	0	5	0
Nephropexy	2	1	1	0	0	2	0
Thoracic operations	9	0	8	1	0	9	0
Intestine and colon	11	0	1	5	5	11	2
Rectovesicle fistula	1	0	0	0	1	1	0
Total	159*	30	71	41	17	158	15

* 158 operations on 144 patients In one case a gastroenterostomy and cholecystectomy was performed at one laparotomy

TABLE V—*Placement of Incisions*

Diseases of	Number Operations	No Data	Incorrect Incision	Correct Incision	Second Incision	Second Operation	Total No Incisions
Appendix	99	34	27	35	6	3	105
Gallbladder	24	6	5	13	1	0	25
Pelvic laparotomy	8	0	0	8	0	0	8
Stomach and duodenum	5	2	0	3	0	0	5
Nephropexy	2	0	0	2	0	0	2
Intestine and colon	10	1	3	5	1	2	12
Thoracic operations	9	0	1	8	0	0	9
Rectovesicle fistula	1	0	0	1	0	0	1
Total	158	43	36	75	8	5	167

revealed that 34 had acute uncomplicated appendicitis nine had appendicitis with peritonitis, six had appendicial abscesses and 23 were questionable having been classified as chronic, interval, normal* or recurring No information is available on the remainder

The diagnosis of situs inversus was made before surgery in 39 cases, during surgery in 24 and several days after surgery in 10

The point of maximum pain was located in the left lower quadrant in 32 cases, in the right lower quadrant in 21 and throughout the lower abdomen in four

* In one of these cases, reported by Michael,⁹⁰ an adherent appendix was removed from the sac during the repair of a left indirect inguinal hernia

A left-sided incision was made in 30 cases (four left McBurney's) a median incision in five and a right-sided incision in 27 (eight right McBurney's) A second correctly-placed incision was made in six cases Of those with an original right McBurney incision a second incision was made in four, the original incision enlarged in three and the abdomen closed without finding the appendix in one

GALLBLADDER

All 24 patients had definite gallbladder disease, 15 had gallstones and six had common duct stones Cholecystectomy was performed in 21, cholecystostomy in two and stones removed from the common duct in seven The pain

TABLE VI—False Pain Projection in Appendicitis and Gallbladder Disease
Location of Pain, Placement of Incision and Time of Diagnosis

Left-Sided Appendicitis												
Location Pain	No Cases	Incision				When Diagnosis is Made						Total
		Right Side	Left Side	Mid- Line	Not Stated	Second Inci- sion	Second Opera- tion	Before Opera- tion	During Opera- tion	After Opera- tion	Not Given	
Pain—left	32	2	25	1	4	0	0	25	4	0	3	32
Not localized	4	3	1	0	0	1	0	2	2	0	0	4
Right	21	16	2	2	1	3	2	4	13	4	0	21
Not stated	39	6	2	2	29	2	1	5	5	6	23	39
Total	96	27	30	5	34	6	3	36	24	10	26	96

Left-Sided Gallbladder Disease												
Pain—left	16	2	9	1	4	1	0	14	2	0	0	16
Midline	1	1	0	0	0	0	0	0	1	0	0	1
Right	2	1	0	1	0	0	0	1	1	0	0	2
Not stated	5	1	2	0	2	0	0	2	2	0	1	5
Total	24	5	11	2	6	1	0	17	6	0	1	24

was located in the left subcostal area in 16, and in the midline in one and under the right rib margin in two The diagnosis of situs inversus was made before operation in 17, during operation in six and after operation in one A correct left-sided incision was made in 11 cases, a midline incision in two and a right-sided incision in five A second incision was required in only one case One author suggests that exposure of the common duct was easier technically through a right-sided incision The case reported by Beck⁷ is of interest because the symptoms were first thought to be due to ptosis of the left kidney Cholecystectomy was finally performed ten days after an unsuccessful left-sided nephropexy

BOWEL SURGERY

Three patients had lesions of the colon Fairchild³⁶ reports the case of a 30-year-old female who was operated on for appendicitis through a right rectus incision An "inflammatory tumor" of the sigmoid was found lying in the right lower quadrant and was resected Total visceral transposition, however,

was not discovered until two years later when roentgen-ray studies were made of the gallbladder

Boeninghaus¹⁶ case is of special interest because, although a total visceral transposition was present, the cecum was in the right lower quadrant as a result of a super-imposed mal-rotation of the bowel. The patient, a 16-year-old male, had a congenital stenosis of the sigmoid and died after ileosigmoidostomy and appendectomy. The diagnosis was confirmed by autopsy.

Lyons⁸² reported the case of a 63-year-old female with right-sided symptoms suggesting appendicial abscess. Operation through a right-sided incision revealed total visceral transposition and diverticulitis of the sigmoid. It is significant that, although most of the pain in this case was on the right, there was some discomfort in the left flank, probably the result of referred phenomenon a condition which will be discussed in detail later.

The two cases reported by Bryan¹⁹ and Maguire,⁸³ both with total transposition, were successfully operated on for adhesive obstruction of the terminal ileum.

In Oehlecker's⁹⁶ case a massive small bowel resection was performed for volvulus. At operation, performed through a midline incision, the patient was found to have a partial transposition with the stomach on the right, the liver and spleen both on the right and the cecum on the left.

Moore⁹² performed three successive ileostomies on a patient with a small bowel obstruction due to ileo-cecal tuberculosis. The author states "adequate drainage at first would probably have made little difference, but had we followed the suggestion from finding the heart on the right side and made an incision and enterostomy on the left our chances would have been better."

Martinez⁸⁷ encountered a 21-year-old male who had a "tumor" in the right lower quadrant. Total situs inversus was discovered and the abdomen was opened through a right-sided incision. The "tumor" was found to be an accessory right-sided spleen with a long pedicle which had produced an obstruction of the ileum.

Tondury and Wissler¹²⁵ reported a case of a ten-day-old infant who was explored because of a mechanical obstruction at the duodeno-jejunal juncture caused by a partial transposition of the stomach and colon.

It is of interest that in this series of 11 cases, three had other congenital anomalies which played a role in the terminal illness.

THORACIC OPERATIONS

Nine operations were performed on seven patients. Smith and Horton¹¹⁶ removed a bullet from the chest of a man who failed in his suicide attempt because he aimed a gun over the usual left precordial area. Vargas¹²⁸ performed repeated pneumothorax treatments on a patient with tuberculosis and LeLong and Meyer⁷⁵ pleuroscoped such a patient with an aortic aneurysm.

Six pulmonary lobectomies were performed on four patients with bronchiectasis. These cases were reported by Ingraham,⁶² Flick,⁴⁰ Lillenthal,⁷⁹ Adams and Churchill.² The fact that 3 per cent of the patients in this series required lobectomy for bronchiectasis conforms with the opinion expressed by Adams

and Churchill that in these individuals there is an increased incidence of bronchiectasis (Kartegner's Syndrome) The ease with which the transposition can be overlooked is emphasized by one case in which the incision was made on the wrong side of the chest in spite of repeated chest roentgenograms and physical examinations before surgery This error resulted from a failure to note the film marking on the roentgen-ray plate

PELVIC LAPAROTOMIES

In the group of pelvic laparotomies there were three uterine suspensions, two hysterectomies, one ectopic pregnancy and two oophorectomies The appendix was removed in three and a perineorrhaphy performed in one All operations were performed through a low midline or Pfannensteel incision The transposition was recognized before surgery in only three instances but the error did not seriously interfere with the surgical procedure

STOMACH OPERATIONS

Five patients were operated on for diseases of the stomach One of these¹⁸ was seen personally in consultation The patient, a 60-year-old male, had a large prepyloric carcinoma of the stomach The visceral transposition was recognized preoperatively by physical and roentgen-ray examinations and confirmed by laparotomy As far as we could determine this was the first case to be recorded in which a successful right-sided subtotal gastric resection had been performed in the presence of this anomaly

Allen³ reported the case of a prepyloric carcinoma in a 30-year-old male who died three weeks after gastro-enterostomy, and Kapustin successfully performed a Billroth I type of partial gastrectomy on a 57-year-old male with a large perforating gastric ulcer

Kelly⁶⁸ performed a cholecystectomy and gastroenterostomy on a 40-year-old female who had both a gastric ulcer and gallstones and King⁷⁰ successfully closed a perforated duodenal ulcer in a 46-year-old Negro The presence of situs inversus did not interfere with treatment in any of these cases

DISCUSSION*

An error in diagnosis occurred in approximately 45 per cent of these cases The transposition was recognized before surgery in 71 (55 per cent) and during surgery in 41 (32 per cent) In 17 (13 per cent) because of the bewilderment of the surgeon the condition was not recognized even at the time of operation In these, the diagnosis was finally made at a later date by roentgen-ray studies

An incorrect surgical incision was made in 36 cases (31 per cent) and in 15 the abdomen was closed without accomplishing the operative procedure In five of the latter the disease process was corrected by a second operation performed after a correct diagnosis had been made

Undoubtedly many of these errors were made because the examining physician, not suspecting the visceral transposition, misinterpreted the signs

* In determining percentages those cases without available information are excluded

and symptoms. This was particularly true in the cases of those individuals with appendicitis—a disease usually considered a surgical emergency and frequently operated on at odd hours of the day, often after only a cursory physical examination. Although the condition can be recognized by physical examination alone, statistics indicate that it is usually overlooked unless roentgen ray studies are made.

FALSE PAIN PROJECTION

An added diagnostic difficulty arises from the fact that many of these individuals complain of pain on the side of the body opposite to that of the diseased organ. This phenomenon has been described in the literature but as yet has not been clearly explained. Pol,⁹⁹ in a smaller series, found that 50 per cent of the patients with left-sided appendicitis complained of pain on the right.

In this series out of 96 patients who were operated on for appendicitis information concerning the location of pain was available only in 57 instances. The pain was located on the right in 21, on the left in 32 and throughout the lower abdomen with no lateral localization in four.

Of the 21 cases with pain on the right, three were classified as chronic, interval or recurrent and three had other pathology to account for the pain, this leaves 15 which are probably examples of false pain projection (Table No. VI). In at least nine of these there was some discomfort in both lower quadrants, although the point of maximum pain was on the right. In Lawrence's case,⁷³ the pain was "mostly on the right except on deep pressure when there was more on the left." Mason and Baker's⁸⁶ case had generalized pain and soreness on the left which shifted to the right.

Of the 32 cases with pain on the left, six were questionable being classified as chronic, interval or recurrent. Acute appendicitis was present in 14, gangrene in four, abscess formation in three and peritonitis in five. Five had typical epigastric distress which localized in the left lower quadrant and five had pain in both lower quadrants more marked on the left.

If this data is rearranged we note that of the 45 cases with definitely proven appendicitis at least 18 had pain in both lower quadrants. The pain was most marked on the right in nine of these and on the left in five. In four there was no lateral localization. The pain was said to be limited to the right side in only six cases and to the left side in 21.

Because of the paucity of available information in these case reports, it is impossible to determine accurately the true clinical picture of appendicitis in these anomalous individuals. There is no doubt however that it is variable and confusing.

VISCERAL PAIN PERCEPTION

The mechanisms of visceral pain perception are not clearly understood—apparently there are three types^{102, 132, 15}

- (1) Referred pain perception as described by Head and McKenzie
- (2) Direct visceral pain perception
- (3) Direct somatic pain perception

TABLE VII—*Left-Sided Appendicitis with False Pain Projection to the Right*

Author	Sex and Age	Pathology	Symptoms	Incision	Time of Diagnosis
Rush ¹⁰⁶	M—18	Acutely inflamed retro-cecal appendix	Ill 48 hours with general cramps nausea and vomiting Pain localized in the right lower quadrant Tenderness right lower quadrant	Right rectus	Suspected before operation
Hemple ⁵⁵	F—9	Acute appendicitis inflammatory changes in the middle third	Ill 1 day General abdominal pains which localized in the right All pain spontaneous as well as pressure in the right lower quadrant	Right pararectal	Operation
King ⁷⁰	F—20	Acute appendix covered with fibrin	Ill 4 days Generalized abdominal pain in both lower quadrants more severe on right	Low midline	Before operation
Uehara ¹²⁷	F—28	Acute plegmonous appendix	Symptoms located on the right	Right rectus	Operation
Block and Michael ¹⁶	F—26	Acute catarrhal appendix, 4 month pregnancy Acute appendix inflamed	Ill 4 hours Pain in the right lower quadrant Slight general rigidity Extreme tenderness in right iliac region	Right McBurney (enlarged)	Operation
Pol Z ⁹⁹	F—8	Acute appendicitis	Pain in the right lower quadrant The constant localization of pain on the right suggested normal location of the viscera	2 incisions right McBurney and left McBurney	Operation
Mason and Baker ⁶⁶	F—13	Acute appendicitis	Ill 24 hours General abdominal pain with soreness in the left lower quadrant which shifted to right Tenderness over entire abdomen more intense on right	Left para median	Operation
Lawrence ⁷³	F—19	Left-sided appendicitis	Ill 12 hours Pain was mostly on the right side except on deep pressure when there was more on left	Right rectus	Confirmed at operation
Lucente ⁸⁰	M—16	Appendicitis Appendix injected high on left	Generalized abdominal pain in both lower quadrants with tenderness and pain in right lower quadrant	2 Incisions Right McBurney Midline	Operation
Scopinaro ¹¹¹	M—30	Acute appendicitis (not proved)	Acute pain in both lower quadrants most marked on right Clinically thought to be appendicitis Appendix not found at emergency operation but an adherent appendix removed six months later	2 operations Right Davis and Midline	Operation
DePol ³⁰	M—35	Appendicitis	Pain around the navel radiating to the right lower quadrant Some pain on left but most severe on right	Left para-rectal	Before operation
Bertone ¹²	F—13	Acute appendicitis	Acute pain in the lower abdomen, right Upon palpation the pain was more rectus conspicuous on the right	Right rectus	Operation

TABLE VII—*Left-Sided Appendicitis with False Pain Projection to the Right (Continued)*

Author	Sex and Age	Pathology	Symptoms	Incision	Time of Diagnosis
Simons ¹¹⁴	F—22	Acute appendicitis General peritonitis	General low abdominal pain more marked on right	Right rectus abdomen closed Appendix not found	Operation
Pool ¹⁰⁰	M—14	Appendicitis with peritonitis	General abdominal pain tenderness and rigidity, more marked on right	2 incisions right para median left McBurney	Operation
Belmes ¹¹	F—17	Pain right lower quadrant Probable acute appendicitis	Pain right lower quadrant	Right rectus Appendix not found	Operation

Left-Sided Gallbladder Disease with Right-Sided Pain

Gonzales ⁴⁸	F—23	Cholecystitis	Indigestion Pain in the upper abdomen radiating under the right rib margin	Right Judd incision	Operation
Wood and Blalock ¹³⁵	F—46	Cholecystitis and lithiasis	Pain in the upper abdomen radiating to the right flank and back	Median	Before operation

In appendicitis occurring in normal individuals the pain is usually first perceived as a vague, mild, generalized epigastric distress which finally localizes in the right lower abdomen. Some authors believe that this right-sided pain is due to referred phenomenon (type 1), while others believe it is the result of direct visceral perception (type 2). As the disease progresses and the parietal peritoneum becomes involved, direct somatic perception may occur.

Evidence suggests that in situs inversus, although the viscera are transposed, the component parts of the nervous system are not reversed.²⁴ Therefore, regardless of the position of the viscera, it is reasonable to assume that their innervation will remain the same. It is for this reason that Block and Michael¹⁵ agree with Kuntz that in appendicitis in situs inversus "*the referred phenomenon ought to be localized on the right side*"

It is suggested in this report that the location of visceral pain in situs inversus might shift from one side of the body to the other, depending on the nervous mechanism which dominates that particular stage of the disease. Right-sided pain may be due to referred phenomenon and left-sided pain to direct visceral or somatic perception. In appendicitis, the pain may start with the usual epigastric distress which shifts temporarily to the right lower quadrant as the result of false projection but finally, as the disease progresses, localizes in the left lower quadrant over the diseased organ. At times during the course of the illness the patient himself might conceivably be confused as to the location of the pain because of the involvement of both mechanisms.

Little is said about the character of abdominal tenderness and related physical findings. Some of the cases are described as having "tenderness in both lower quadrants, more marked on the right" or "more marked on the left."

Others are said to show general tenderness with no lateral localization. Lawrence's⁷³ case had more pain on the right but more tenderness on the left. In the cases of Block and Michael¹⁵ and Curt Hempel⁷⁷ tenderness as well as pain was said to be on the right. The disease in both of these was early and the transposition was not discovered until the abdomen was opened. It seems logical to assume, however, that the maximum point of tenderness should be located directly over the diseased organ but from the available information it is impossible to determine whether in the early stage of the disease pain produced by left-sided pressure might be projected to the right side.

In order to clarify this confused clinical picture, the suggestion is made that surgeons who in the future are privileged to see a patient with situs inversus and appendicitis report a detailed description of the history and physical findings with the points of this discussion in mind.

SUMMARY

In a collective review of the literature, an analysis is made of the available data in 144 cases of situs inversus in which 158 surgical operations were performed.

There were 99 operations for appendicitis, 24 for gallbladder disease, five stomach operations, eight pelvic laparotomies, two nephropexies, 11 operations of the large and small bowel, one repair of rectovesical fistula and nine thoracic operations including six lobectomies for bronchiectasis.

The difficulty in recognizing situs inversus is emphasized by the fact that an incorrect preoperative diagnosis was made in approximately 45 per cent of the cases and as a result in 31 per cent an incorrect surgical incision was made. False projection of pain to the opposite side of the body was present in at least 33 per cent of the cases of left-sided appendicitis and 8 per cent of the cases of left-sided gallbladder disease.

Considerable confusion exists regarding the phenomenon of false pain projection in patients with this anomaly. Accepting the theories of Kuntz and reasoning along the lines of Block and Michael, the suggestion is made that patients with appendicitis may have pain in both lower abdominal quadrants. In the early stages of the disease pain may be projected falsely to the right side, but as the disease progresses true localization will occur on the left over the diseased organ.

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FACTORS IN THE MORTALITY OF THE RUPTURED APPENDIX*†

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In a report¹ compiled for the years 1931–1937 inclusive and representing a study of 1412 consecutive cases of all types of appendicitis it was found that those cases complicated by perforation had a mortality of 15.3 per cent. The unruptured group carried a mortality of less than 2 per cent during this period. Any appreciable reduction in overall mortality must therefore be directed toward the perforated group.

The material in this report is derived from the perforated cases which were admitted to the hospital from 1942–1947 inclusive. The year 1942 was chosen as a starting point because the general use of the sulfonamide drugs was instituted in that year in this hospital. A total of 183 cases of perforated appendices were found in the records and in addition 65 cases of gangrenous appendicitis with local peritonitis were analyzed in this six-year period. All cases were admissions to the Muhlenberg Hospital which is a general hospital in a suburban community with a rated capacity of 330 beds.

It can be seen from the two tables submitted that there has been a reduction of 6.6 per cent in the perforated group for the years 1942–47. This decrease in mortality is probably not due to any single factor in the management of the appendicitis problem but it is difficult to escape the conclusion that the sulfonamides and antibiotics played a major role in effecting this reduction. Other factors which might be mentioned include

- (a) Better appreciation of the problems of fluid requirements and vitamin deficiencies
- (b) Improved methods of anesthesia
- (c) Advent of tube decompression of the intestinal tract
- (d) Educational methods to acquaint the patient with the danger of delay, catharsis, etc

One hesitates to make any definite statement concerning the effects of early ambulation on the mortality rate inasmuch as it has been utilized only in the non-perforated group in this hospital.

Other published reports have generally shown a waning mortality in this disease in recent years. Tashiro and Zininger² in a review of 936 cases at the Cincinnati General Hospital found that the mortality in the perforated group was 13.77 per cent between the years 1939 and 1943. This is to be com-

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pared with their previous figures of 17.2 per cent (1934-38) and 33.9 per cent between 1915 and 1934. Schullinger³ studied results at the Presbyterian Hospital, N. Y., and classified the cases complicated by perforation into three main groups which he defined as the acute progressive fibrino-purulent peritonitis, the acute diffuse peritonitis and the peritonitis with abscess. In the years 1941-46, 10 deaths occurred which gave them an average mortality of 6.6 per cent for the three groups mentioned.

TABLE I

Year	Perforated	Deaths	Mortality	Gangrenous	Deaths	Mortality
1942	33	2	6.0%	5	0	0
1943	20	3	15.0%	14	0	0
1944	27	4	15.0%	12	0	0
1945	32	4	12.5%	10	0	0
1946	45	2	4.4%	17	0	0
1947	26	1	3.8%	7	1	14.2%
Totals	183	16	8.7%	65	1	1.5%

Average mortality for ruptured cases 1942-47 is 8.7%

Average mortality for acute gangrenous cases 1942-47 is 1.5%

TABLE II

Years	Perforated	Deaths	Mortality
1931-1937	165	26	15.3%
1942-1947	183	16	8.7%

Meyer *et al.*⁴ reported on their experience at the Cook County Hospital in Chicago. In the two years 1944 and 1945 they studied 136 perforated cases and found the mortality to be 13.9 per cent.

Kaufman and Mersheimer⁵ tabulated 92 ruptured appendices from June 1940 to December 1941 at the Metropolitan and Flower Hospitals in New York City. The sulfonamides had been used in the therapy and with 10 deaths their mortality rate was established at 10.8 per cent.

The highest mortality occurred in the 7th and 8th decades as would be the normal expectancy. The appendix at this age has undergone considerable fibrosis with a diminution of blood supply and consequent inability to build up local defenses against the infection. The devitalized appendix is also more prone to perforation. The mortality in the 4th decade is surprising when it is noted that it is much lower in the 5th and 6th.

CATHARSES AND ENEMATA

Since the publication of the last series the public has been informed by various means that active purgation is a dangerous course in the presence of abdominal pain. Although the figures in this respect are not entirely conclusive due to the failure of accurate recording on the charts, a tabulation showed that 8.1 per cent of the perforated cases had taken a cathartic of some sort previous to admission. This figure is a marked decrease from the 23 per cent

of the former series. Thirteen per cent had received a rectal irrigation as compared to the previous figure of 10 per cent. There seems to be no definite hazard from rectal irrigation when it is not massive and when the diagnosis of appendicitis is uncertain.

DRAINAGE

No flat statement can be made from our figures as to the value of drainage. In the years 1942-45 100 per cent of the cases were drained, but in the next two years (1946-47) there was a drop in the cases drained to approximately 82 per cent. This would seem to indicate that the operators were beginning to doubt the efficacy of drainage when the peritoneum was contaminated.

Jackson⁶ has recently advocated the principle of nondrainage in the perforated appendix and cites 15 cases of perforated appendicitis in which the

TABLE III

Age Distribution Age	No. Cases	Deaths	Percentage Mortality
0-1 year	0	0	0
1-9 year	29	1	3.4
10-19 year	77	5	6.5
20-29 year	26	0	0.0
30-39 year	29	0	0.0
40-49 year	33	6	18.2
50-59 year	29	1	3.4
60-69 year	14	0	0.0
70-79 year	7	2	28.5
80-89 year	4	2	50.0

appendix was removed and closure was done without drainage. One secondary abscess occurred which required drainage but there was no death in this series. He stressed the disadvantages of prolonged drainage with attendant wound infection, adhesions, fistulae, herniae, *etc*.

On the other hand Schullinger³ advocates intraperitoneal drainage under the following conditions:

- (a) Abscess
- (b) Presence of necrotic tissue which cannot be readily excised
- (c) Appendix not removed
- (d) Extensive exposure of retroperitoneal tissue
- (e) Insecure ligation of the stump

HOSPITAL DAYS

There has been some decrease in the length of the hospital stay for the perforated cases. The average length of time for the years 1931-37 amounted to 23.2 days while the recent series averaged 20.7 days.

A greater decrease in hospital days was anticipated. This small decrease might be explained on the basis that some desperately ill patients underwent a prolonged convalescence who might have terminated fatally if improved methods of therapy had not been available.

As has been previously stated those perforated cases who ran a febrile course and leukocytosis were not encouraged to practice early ambulation until their fever had subsided. Whether early ambulation would have decreased their hospital stay is debatable.

SULFONAMIDE — ANTIBIOTIC THERAPY

Approximately 88 per cent of the perforated cases had implantation of the powdered sulfa drug in the peritoneal cavity at the time of operation. The amount of drug used varied greatly among the different operators with an average of from 3 to 10 Gm. Some form of the sulfa drug was given orally in 41.3 per cent of all cases while 43.7 per cent received it intravenously buffered with sodium lactate. The intravenous dose was a subject of some debate but many operators have felt that if it was to attain an adequate blood level as much as 7.5 Gm. should be administered over a 24-hour period. No serious complications have resulted from the use of this dosage.

Penicillin was first used in 1944. There was a rapid increase in this mode of therapy in the last three years when approximately three-fourths of all perforated cases received the drug. The intramuscular route has been favored over the oral or intraperitoneal route.

The use of streptomycin has been very limited. Of three cases in which it was used two recovered and one terminated fatally. It was used in conjunction with the two previously mentioned drugs which makes its evaluation difficult but there does seem to be a question whether the dosage of 600 mgs per day was adequate.

THE ROLE OF CONSERVATISM

As a general rule laparotomy was performed when the diagnosis of appendicitis was established. A delay was indicated if the patient was dehydrated markedly or in a near moribund state.

An exception to this rule was carried out in a selected group of patients who upon admission presented a palpable right lower quadrant mass and who seemed to have walled off their perforation. On the assumption that surgery would possibly interfere with the local defense mechanisms set up by the body, these patients were watched carefully for change in size of the mass. Therapy consisted of moderately heavy doses of sulfa drug, penicillin, streptomycin, intravenous fluids, sedatives, *etc.* This regimen was carried out on a total of eight patients without any mortality which would seem to justify its continuance in this type of case. On discharge the patient is warned as to probable recurrence and urged to return at the expiration of four months for appendectomy.

The experience of Meyer *et al.*,⁴ at Cook County Hospital has indicated that whenever a mass is definitely palpable in the region of the cecum operative interference carries a higher mortality. They cited 75 cases which they felt represented abscess formation. Twelve of these patients were subjected to operation with an eventual mortality of 8.5 per cent while the remaining 63

patients were treated by non-operative means and carried the lower mortality of 31 per cent. It should be noted that these figures are drawn from the years 1944 and 1945.

THE CHRONIC APPENDIX

An incidental finding in this review was the infrequency of the diagnosis of "chronic" appendicitis. Whereas in the series from 1931-1937 the ratio of acute and chronic appendices was about one to one, it is now found that the

TABLE IV

Complications	Number of Cases
Dermatitis presumably due to sulfonamides	2
Fecal fistula	6
Grossly infected wound	6
Intestinal obstruction	6
Diabetes mellitus (diagnosed pre operatively)	3
Bronchopneumonia	3
Pulmonary embolus	2
Ruptured appendix in inguinal hernia sac	1
Pregnancy (3 months)	1
Evisceration	2
Atelectasis	1
Hemorrhage from ileostomy	1

pathologic diagnosis of an acute process occurs in the ratio of eight to one of the "chronic" type. The pathologic picture of the chronic appendix has never been clear cut. Soreness in the right lower quadrant along with gastro-intestinal complaints such as gas and constipation have often made up the clinical picture, but there is a growing tendency to believe that the history should include the signs and symptoms of a more or less acute infectious process.

TABLE V

Types of Incision	
1 Right rectus	230
2 McBurney	9
3 Extra peritoneal approach	2

TABLE VI

Anesthesia	
1 Inhalation (general)	195
2 Spinal	42
3 Pentothal sodium	1

INCIDENCE OF PERFORATION

Approximately 11 per cent of all patients with pathology in the appendix had perforation on admission. The 1931-1937 series also showed about this same incidence. It would be expected that the percentage of perforated cases would be lower due to better information possessed by the public as to the haz-

ards of abdominal pain Since the exact time of the perforation is not easy to deduce, it must be assumed that perforation may take place very early in the course of the disease and in some instances may even occur with the onset of symptoms

COMPLICATIONS

Table IV lists only the major postoperative complications

Of the six fecal fistulae listed in Table IV only two closed spontaneously, at the expiration of 21 and 23 days respectively In the third case a fistula was present in the patient who expired on the 44th postoperative day The fourth instance of a fistula persisted in a patient who had had an incision and drainage in the right lower quadrant This fistula was explored and found to lead to the tip of the appendix and following removal of the appendix the fistula remained closed The fistula in the 5th case required two operative attempts at closure The first attempt was done 10 weeks following the original appendectomy and although the fistula was dissected down to its apparent terminus in a loop of the small bowel it failed to close One year later it was again dissected out and remained closed In the final case there is a question whether the fistula was a result of an appendiceal abscess On admission to the hospital a stab incision was made and the abscess in the region of the cecum was thereby drained Inasmuch as the drainage area did not remain closed but reopened in three weeks, further exploration was done and an extensive carcinoma of the cecum was found

DEATHS

A summary of the deaths with the terminal diagnosis is given in Table VII

Thus it can be seen from Table VII that 16 deaths occurred in the perforated group In 11 of these the appendix was removed at operation while in four others a simple incision and drainage was done without appendectomy One case had no surgery inasmuch as he was deemed too poor an operative risk on account of his cardiac condition The diagnosis in this case was proved at autopsy The one death in the non-perforated group occurred in a 19-year-old female At autopsy on the 10th postoperative day a saddle type pulmonary embolus was found

The largest number of deaths, six, occurred in the 40-50 year old group The youngest casualty was a 9-year-old male, while the oldest were two individuals at the age of 84 years

SUMMARY

I A study of 183 cases of perforated appendices has been made The majority of these cases received some form of chemotherapy and a mortality rate of 8.7 per cent has been determined for the whole group This mortality rate represents a reduction of 6.6 per cent from a previous report of 165 cases not treated by chemotherapy published 10 years before

2 The group in the late stages of perforation have seemed to do better with non-operative therapy. This group usually carry the highest mortality as compared with the group whose perforation is recent. The early perforated group as a rule are subjected to immediate operative therapy.

TABLE VII

Deaths		Type of Surgery	Hospital Duration		Terminal Diagnosis
Sex	Age		Days	Symp	
1 F	51	Inc and drainage	1	1	Cardiac decompensation—general peritonitis
2 M	16	Appendectomy	6	1	General peritonitis with intestinal obstruction
3 M	11	Appendectomy	1	1	General peritonitis
4 M	84	Appendectomy	3	6	Appendix contained within an irreducible right inguinal hernia sac
5 M	46	Appendectomy	5	5	Gangrenous cecum with general peritonitis
6 M	44	No operation	3	7	General peritonitis (poor operative risk with history of coronary thrombosis)
7 M	49	Appendectomy	3	4	General peritonitis
8 F	44	Inc and drainage	2	3	General peritonitis
9 M	42	Inc and drainage	44	2	Broncho pneumonia—fecal fistula—general peritonitis
10 F	49	Inc and drainage	4	5	General peritonitis
11 M	75	Appendectomy	3	7	Hypertension—auricular fibrillation and general peritonitis
12 F	10	Appendectomy	6	7	General peritonitis
13 F	9	Appendectomy	1	2	General peritonitis
14 F	70	Appendectomy	2	3	Diabetes mellitus and general peritonitis
15 F	84	Appendectomy	2	3	Pulmonary embolism
16 M	15	Appendectomy	7	3	Intestinal obstruction on 6th day with exploration on 17th day
Gangrenous Case Mortality					
17 F	19	Appendectomy	10	1	Pulmonary embolus

3 There is still opportunity for considerable improvement in the mortality figures herewith presented.

4 Removal of the nonperforated gangrenous appendix carries a low mortality even though some degree of local peritonitis may be present.

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NEUROFIBROMA *

BENIGN INTRASPINAL-INTRATHORACIC "HOUR-GLASS" TUMOR WITH PARAPLEGIA

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INTRODUCTION

The therapeutic effect of roentgen rays on certain malignant tumors of the body is well known. Not infrequently mediastinal masses have been subjected to roentgen-ray therapy and the response to this treatment used as an indication of the malignancy of the lesion. Benign tumors show no diminution in size following such treatment and, as has been recently reported by Simpson,¹⁰ may be left for years without removal. Benign tumors may become malignant over the course of months or years and it is wise to remove or at least to biopsy all such tumors. Tumors involving the central nervous system either the brain or spinal cord, however, should never be subjected to a therapeutic trial of roentgen-ray before biopsy or before decompression of the tumor.⁵ Both the spinal cord and the brain are enclosed in bone and irreversible changes may occur in these structures secondary to the pressure of tumors resulting from unnecessary delay in their removal. Furthermore, even known malignant tumors involving the central nervous system should not be radiated prior to operation since the swelling that results from therapy may be sufficient to cause permanent paralysis or death. Ward and Spurling¹¹ have taken exception to this rule in the surgical treatment of tumors of the third ventricle advocating subtemporal decompression to reduce intracranial pressure and preserve vision and a trial of roentgen-ray therapy. Because of the high morbidity and mortality associated with removal of tumors in and around the third ventricle and because of the satisfactory response of some of these tumors to roentgen therapy, such a course may be justified, a subsequent surgical removal of tumors not responding to roentgen-ray being carried out in those patients deemed suitable for surgery. This is a highly specialized problem and does not vitiate the argument against the radiation of other tumors involving the central nervous system without preliminary histological verification.

Particular danger is inherent in the utilization of the roentgenographic appearance of a tumor as an index of its malignancy. The presumption that a tumor is incurable because of its size, appearance, and response to roentgen therapy may deprive an individual of the curative value of successful surgical therapy. The following case is illustrative of the potential danger and its successful outcome serves to further emphasize the need for careful consideration of these problems.

* Submitted for publication, October, 1948

CASE REPORT

S F Male Age 35 C 15540

Chief Complaint Paralysis of legs, five months

Family History Non-contributory

Past History No previous nervous disorders Mild chronic cough but no significant amount of sputum

Present Illness In August, 1947, this patient, a farmer, visited a travelling "Chest Clinic" where a roentgenogram was taken. He was told that he had a tumor in his chest and was advised to see his physician. He disregarded this advice but about one month later, in September, 1947, he first noticed slight weakness of his right leg. During



FIG 1 —Roentgenogram of chest showing large rounded mass in left upper thoracic cavity

the succeeding two months the weakness of the right leg became more severe and his left leg also became weak. In November, 1947, he had to stop work because of the weakness of his legs. He had had no pain in his back, chest or legs and at that time suffered no urinary hesitancy or incontinence.

The patient sought the help of a chiropractor but the treatments he received did not increase the strength in his legs. He then sought the help of a physician who in December, 1947, arranged for admission of the patient to the Toronto General Hospital. The patient, however, refused to keep this appointment and remained at home until February 21, 1948.

NEUROFIBROMA

During the two months prior to admission to the hospital he became completely bedridden and about one week before he finally came to the hospital, he became incontinent of urine and feces. A diagnosis of carcinoma of the lung was made and the patient was sent to the Radiotherapy Unit of the Toronto General Hospital.

There had been only a slight weight loss. He had had no hemoptysis.

Physical Examination Temperature 98° F, pulse 80, respirations 16, blood pressure 128/80. The patient was well developed but thin. He was unable to sit or to stand because of weakness of muscles below his waist. The skin and subcutaneous tissues showed no abnormalities. Examination of the heart and lungs showed nothing abnormal.



FIG 2—Roentgenogram of thoracic spine and ribs. There is destruction of the head and neck of the fourth rib on the left with absence of the pedicle of the fourth dorsal vertebra on that side. Note trabeculated appearance of region in which rib is destroyed.

Neurologic Examination Cranial nerves, spine and upper extremities normal. Sensory examination showed slight hypesthesia to pin-prick below the sixth thoracic dermatome level, this abnormality being more marked on the right than on the left. The exact upper limit of this was difficult to determine.

There was weakness of all muscles below the upper abdominal region and bilateral foot drop. Weakness was much more pronounced on the left than on the right. The knee and ankle responses were hyperactive on both sides and there was bilateral sustained ankle clonus. Babinski responses were positive bilaterally.

There was complete paralysis of bladder function, an indwelling urethral catheter with tidal irrigator being necessary, and the tone of the anal sphincter was absent.

Laboratory Data Hemoglobin 98%, white blood count 11,000, urine examination normal, blood Wassermann negative, blood N P N 42 mg %

Course in the Hospital A roentgenogram of the chest disclosed a large discrete rounded mass in the left upper chest posteriorly measuring about 8.0 cm in diameter (Fig 1). There was destruction of the head and neck of the left fourth rib. Films of the thoracic spine showed loss of the pedicle of the fourth dorsal vertebra on the left side and erosion of the pedicles of the vertebrae immediately above and below the fourth vertebra (Fig 2).

The patient was seen in consultation by the Surgical Service. It was felt that the appearance of the roentgenograms was unusual for a benign tumor. The tumor was considered to be a bronchogenic carcinoma with invasion of the fourth rib and secondary involvement of the spinal cord. Aspiration biopsy was advised. Two attempts at biopsy through needles specially designed for the purpose of biopsy were made, one on February 28, 1948, and one on March 9, 1948. Tumor tissue was not obtained in either biopsy.

On March 1, 1948, radiation therapy through anterior and posterior portals directed to the intrathoracic portion of the tumor was begun. This was continued to March 29, 1948, an estimated total of 3,000 roentgen units being delivered to the tumor.

During the period of roentgen therapy and immediately following it the patient showed a progressively more severe paraplegia so that by April 5, 1948, he was barely able to move his toes and could not bend his knees. A roentgenogram of the chest showed little or no change in the size of the tumor.

Arrangements were made for transfer of the patient to a home for incurables, it being felt that he was suffering from a malignant tumor which was inoperable and insensitive to roentgen-ray therapy. Before transfer of the patient to the home for incurables was effected, a consultation with the Neurosurgical Service was held. Operation was advised but because of the radiation skin reaction adjacent to the proposed operative site, this was delayed from April 12 to April 21.

Operation April 21, 1948. A laminectomy of the second through the fifth dorsal vertebrae was done. Tumor tissue was encountered herniating through the laminae of the third and fourth dorsal vertebrae on the left side. The tumor was an encapsulated extra-dural mass and the intraspinal portion was completely removed. It extended out through the fourth left intervertebral canal into the chest, the neck of the tumor at this point measuring about 2-3 cm. The dura was opened and the spinal cord was normal except for a slight pressure defect at the point of maximum pressure from the extra-dural tumor. The dura was closed with silk and the wound was closed in layers with interrupted sutures of silk. The wound healed by primary intention and the patient noticed improvement in the sensation of the skin below the level of the tumor within three days after operation. Within two weeks the strength of the legs had increased greatly and the improvement was easily discernible. He began to suffer suprapubic discomfort and was discovered to have a vesicle calculus. This was removed through a cystoscope on April 29, 1948.

Operation May 10, 1948. Through a left posterior thoracotomy incision, the left third, fourth and fifth ribs were partially resected and a large intrathoracic, extra-pleural, encapsulated tumor was removed. The portion of the spinal canal from which the intra-spinal tumor had been previously taken was clearly visualized. All visible tumor was removed.

Postoperative Course The patient made a satisfactory recovery from this operation and the wound healed satisfactorily. His neurologic improvement continued and by May 25, 1948, slightly more than one month after laminectomy, he was able to walk with help. Bladder and bowel control had been regained and were now practically normal. There was 30 cc of residual urine on catheterization. Seven weeks after laminectomy the patient was able to walk alone with one cane and was discharged to a convalescent home for paraplegics for continued physiotherapy and training.

August 30, 1948, three and one-half months after removal of the intraspinal portion of the tumor, the patient could walk normally and showed no objective weakness of his legs. Neurologic examination showed no sensory abnormalities. Knee and ankle jerks were slightly hyperactive, there was no ankle clonus, and the plantar responses were normal. He reported that sexual function was normal. He was at that time ready for discharge to his own home where he could resume light farm work.

Pathologic Report Microscopic examination—the tumor was composed of cells which were fibroblastic in type, arranged in sweeping bands and occasionally in whorls. The tissue was moderately cellular but showed no evidence of malignancy.

Diagnosis Benign neurofibroma or perineurial fibroblastoma (Fig. 3)

DISCUSSION

Hour-glass tumors located in part in the spinal canal and in part in the thoracic cavity are not common but there have been several reports of such

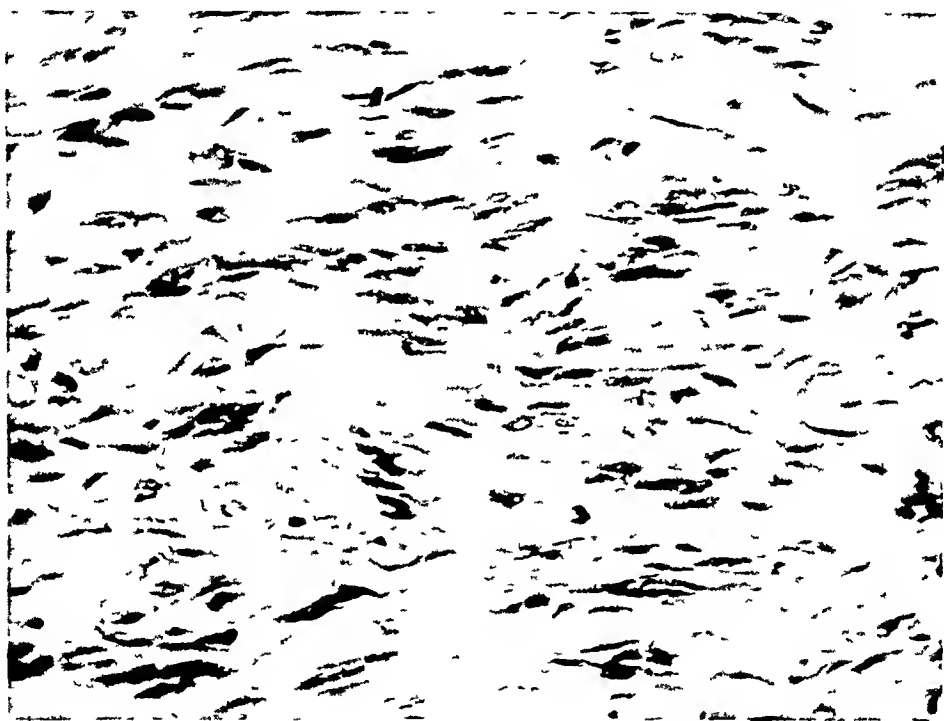


FIG. 3—Photomicrograph of the tumor showing fibroblasts arranged in sweeping bands and occasional palisade formation. There is no evidence of malignancy.

lesions in the literature of the last two decades.^{2, 3, 4, 6, 7, 8} A number of different histologic tumors have been described but the majority of these tumors are benign. Most common of the lesions found in this particular location is the perineurial fibroblastoma or neurofibroma.

Several features of the case reported above are of particular interest and warrant consideration. The roentgenologic appearance of the tumor, particularly the involvement of the head and neck of the left fourth rib by what seemed to be a destructive process, is unusual for this type of tumor. A somewhat similar appearance was described by Carman and Davis¹ in 1924 in a patient who presented the roentgen-ray picture of a trabeculated cyst in one of the

lower dorsal vertebra. The lesion in their case was also a neurofibroma. No other cases have been found with roentgenographic features similar to this.

In 1941 Powles⁹ in New Zealand reported a case which has an interesting analogy to the case reported in this publication. The patient described by Powles was also paraplegic and presented with an intrathoracic as well as an intraspinal tumor. Because of the roentgen-ray appearance of the lesion, a diagnosis of carcinoma of the lung with metastases to the spine was made and no treatment was given. The paper did not contain reproduction of the roentgen-ray films. The progress of the lesion was so slow that those who were caring for the patient eventually questioned the diagnosis of a malignant tumor. By the time this question was raised, however, the individual was completely paraplegic and was not considered a suitable subject for surgery. He died of *urinary tract infection and decubitus ulcers* approximately $2\frac{1}{2}$ years after the onset of his spinal cord symptoms. Post mortem examination showed a benign extramedullary neurofibroma at the level of the seventh cervical vertebra with extension of the tumor into the thoracic cavity. There was no evidence of malignancy. The exactly similar course of the patient reported herein was fortunately interrupted by the earlier suspicion of the benign nature of the lesion and the institution of surgical therapy.

In view of the profound degree of motor loss extending over a prolonged period of time, the rapid and almost complete recovery of motor, sensory, urinary, bowel and sexual function in this patient was not altogether anticipated and was particularly gratifying. Within four months he progressed from a state of severe paraplegia necessitating constant bed care to the recovery of such function that he was able to return to light farm work. It might be expected that his recovery will continue toward a normal state for some months and no recurrence is to be expected in view of the complete removal of what proved to be a benign lesion.

SUMMARY

1 A patient with a benign neurofibroma of the "hour-glass" type, involving the dorsal spine and the thoracic cavity has been presented.

2 The unusual roentgenographic appearance of this tumor has been demonstrated. This suggested a malignant tumor and an initial diagnosis of a bronchogenic carcinoma with invasion of the ribs and spine was made.

3 The patient was subjected to intensive radiation therapy directed to the intrathoracic portion of the tumor without perceptible effect.

4 Rapid recovery of the patient after complete surgical removal of the tumor has been described.

5 The danger of subjecting any tumor causing spinal cord compression to radiotherapy without biopsy has been re-emphasized.

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GUMMA OF THE LUNG

REPORT OF A CASE TREATED BY LOBECTOMY*

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ACQUIRED SYPHILIS OF THE LUNG is a rare disease. Wilson stated recently that only a small percentage of approximately 200 reported cases have been confirmed at autopsy.¹⁴ Several authors have subgrouped this disease according to its pathologic manifestations.^{1, 6, 9} The different classifications offered are not in complete agreement, but it is recognized generally that gumma of the lung is an unusual type of pulmonary syphilis.¹⁴

The treatment of gumma of the lung in the past has been medical. Arsenicals, iodides, bismuth compounds and mercurials have been given to affected patients with varied success. Penicillin has been used more recently.⁸ Since surgical excision of a pulmonary gumma has not been considered as a form of therapy, the following case is presented as an example of the operative treatment of this disease.

CASE HISTORY

J W, No 888615, a 39-year-old Negro male, entered the Presbyterian Hospital, New York, on October 27, 1947, because of left chest pain and cough of 5 weeks' duration.

History He had a penile lesion at the age of 18 at which time he was given simultaneous injections into his hip and arm on three occasions. Three years before admission to the hospital his physician gave him 3 injections into his hip over a 6 day period because he was found to have a positive Wassermann.

He had no significant complaints until 5 weeks before admission when he had chill sensations associated with pain in the lower left chest. This pain was dull in character, but it was aggravated by deep breathing and lying on the affected side. He soon developed a persistent cough productive of small amounts of yellow, non-foul, non-bloody sputum. His local physician noted an area of increased density in the lower lobe of the left lung by fluoroscopy. He made the diagnosis of virus pneumonia for which he prescribed cough medicine. This treatment produced temporary relief of the patient's cough, although the pain continued without increasing in severity. He began to feel moderately weak, and had occasional slight malaise. Over the 5-week period he lost 10 pounds in weight. He had no fever, chills or night sweats except at the onset of the illness.

Physical Examination T-98.4 P-75 R-18 BP 115/80. The patient was a well developed, well-nourished Negro male who was not in acute distress and showed no obvious signs of chronic illness. The following pertinent findings were noted. The examination of the eyes revealed nothing unusual. The teeth were grossly carious. There was no generalized glandular enlargement. The chest expanded symmetrically. Dullness was

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noted over the lower lobe of the left lung posteriorly, and tubular breathing with fine crackling inspiratory rales were heard over the same area. Both diaphragms descended equally and well. The liver, spleen and kidneys were not felt. A rectal stricture was noted on digital examination. The neurological findings were normal.

Laboratory Data The urine was negative. The red blood cell count was 4.4 million, hemoglobin, 13.4 Gm per cent, white blood count, 12,650 with 61 per cent polymorphonuclear leucocytes, 37 per cent lymphocytes and 2 per cent eosinophiles. A tuberculin test in 1:10,000 dilution was negative but positive in 1:100 dilution after 48 hours. The blood Kline and Wassermann tests were four plus to all antigens. The stool was negative for blood, ova and parasites. No acid fast bacilli were seen in the sputum, although pneumococci type VI were cultured from it. The blood was negative for cold agglutinins and the erythrocyte sedimentation rate was 130 mm per hour. The Frei test was positive. The serum albumin was 4.3 Gm per cent, globulin, 4.5 Gm per cent, euglobulin 1.1 Gm per cent, the blood urea nitrogen 17 mg per cent, serum calcium, 10.8 mg per cent, inorganic phosphorus, 4.8 mg per cent, alkaline phosphatase 3.1 Bodansky units. The cephalin flocculation was negative and the thymol turbidity was 3 plus.

A lumbar puncture revealed an initial pressure of 165 mm of spinal fluid. The microscopic examination of the fluid was not remarkable, the spinal fluid protein was 27 mg per cent. The colloidal gold curve was flat and the spinal fluid Wassermann was negative to both the cholesterin and alcoholic antigens.

TABLE I—Summary of Treatment, Procedures and Hospital Course (See Text)

	Days After Admission
Admitted	0
Attempted thoracentesis	2
Fluoroscopy	4
Lumbar puncture	6
Bronchoscopy	8
	10
	12
	14
	16
	18
Decrease in size of pulmonary lesion noted for first time roentgenographically	20
	22
	24
	26
No further reduction in size of lesion noted on films	28
	30
	32
Left lower lobe lobectomy	34
	36
	38
	40
	42
Discharged	44

Penicillin 400,000 U Daily

I Lugol's Solution 25-30 cc Daily
I Iunctionin 1,000,000 U Daily

Penicillin 400,000 U Daily

Roentgenologic Findings Roentgenograms of the chest taken on admission showed a well defined, lobulated area of increased density located posteriorly and medially in the left hemithorax (Fig 1) The shadow appeared to occupy the dorsal apical and posterior basal divisions of the left lower lobe The lung fields elsewhere and the heart were normal It could not be determined whether this was a parenchymal lesion or a loculated collection of fluid

A roentgenogram taken one week later showed no change in the shadow Fluoroscopic examination at this time demonstrated movement of the lesion on respiration suggesting that the process was intrapulmonary Spot films revealed considerable thickening of the pleura over the lateral aspect of the lower lobe on the left

Course The patient's only complaints on admission were persistent cough and mild left chest pain To rule out a loculated pleural effusion, a needle was inserted into the left pleural cavity at an appropriate site, but no fluid could be obtained On the fifth hospital day parenteral penicillin was administered to determine its effect on the size of

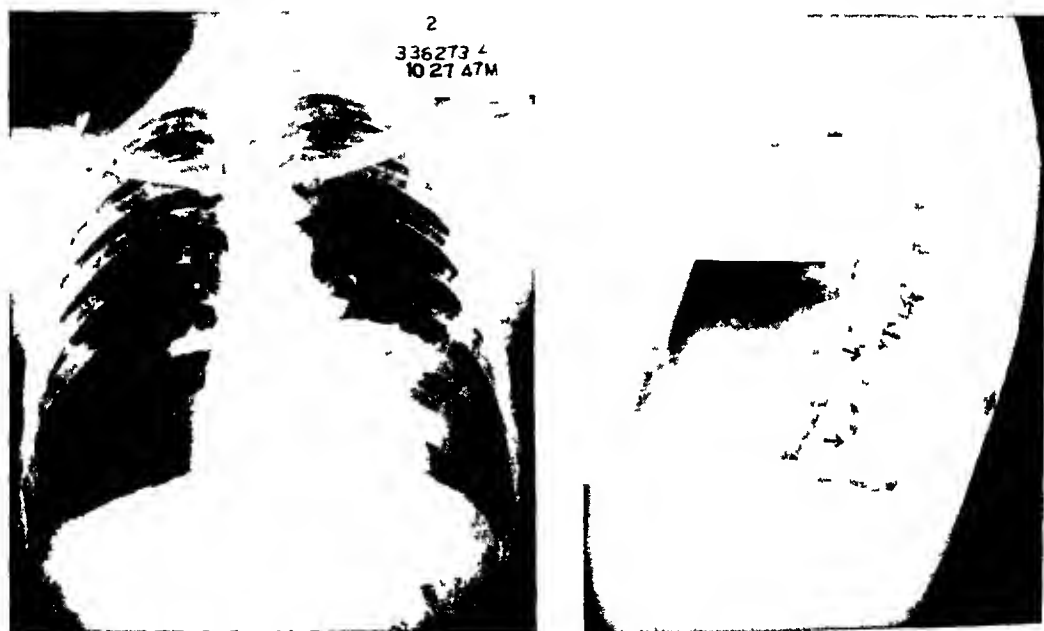


FIG 1—Gumma of lung, postero-anterior and left lateral projections

Admission films (21 years following penile lesion) disclose a well-defined, lobulated, mottled area of increased density in the dorsal apical and posterior basal segments in the lower lobe of the left lung

the chest lesion Four hundred thousand units of the drug were given daily by the intramuscular route for 12 days The clinical course of the patient continued to be benign His cough and chest pain were less bothersome, but another roentgenogram at the end of this period was not significantly different than the one taken on admission A bronchoscopic examination was performed on the 13th hospital day The findings were normal except for slight, diffuse injection of the bronchial mucosa bilaterally

Considering the history of lues, the positive serology, and the unusual contour of the pulmonary shadow, the diagnosis of gumma of the lung was contemplated Accordingly, the dosage of the parenteral penicillin was increased to 1,000,000 units a day and this was administered for two weeks Between 25 to 30 cc of Lugols solution were also given daily over approximately the same period The above treatment was instituted with two purposes in mind It was thought advisable in the first place to treat his latent syphilis Secondly, the pulmonary lesion could be studied by roentgen-ray examination for its response to therapy

GUMMA OF THE LUNG

Roentgenograms of the chest were taken on the 19th hospital day and diminution in the size of the lesion was noted for the first time. A review of all the films showed that the volume of the lower lobe of the left lung was progressively decreasing with elevation of the left diaphragm. Roentgenographic studies nine days later, however, demonstrated no further decrease in the size of the lesion (Fig 2).

Repeated physical examinations revealed essentially the same findings as noted on admission. The patient never had any significant changes in his temperature, pulse or respiratory rate. His cough and chest pain practically disappeared, and there was considerable improvement in his general well being.

After one month of medical treatment, surgical and medical consultants were of the opinion that the therapy instituted thus far had not produced a satisfactory response. The diagnosis had not been established definitely, and the presence of a neoplasm could not be ruled out. An exploratory thoracotomy and a left lower lobe lobectomy were performed, therefore, on the patient's 34th hospital day.



FIG 2—Gumma of lung, postero-anterior and left lateral projections

Films made 30 days after films in Figure 1 (25 days after penicillin therapy) disclose a slight decrease in size of the mass, with the anterior border more sharply defined, as seen on the lateral film.

Diagnosis Throughout this patient's hospitalization, studies were directed to determine whether the underlying pulmonary pathology was inflammatory or neoplastic and most of the evidence seemed to favor the former category. For reasons stated previously, a granulomatous or gummatous pulmonary lesion caused by syphilis was entertained. The rarity and lack of characteristic diagnostic findings in gumma of the lung made this diagnosis seem unlikely when the incidence and varied clinical picture of pulmonary neoplasms was considered.

Operative Procedure and Findings The left pleural cavity was entered posterolaterally through the bed of the 8th rib. A markedly thickened, adherent, and extremely vascular pleura with small yellow plaques was encountered posteriorly. There were less dense adhesions over the diaphragm. After the left lower lobe had been freed of all its pleural attachments, it was found to be reduced to half its normal volume. The lobe aerated normally except for the posterior basal division which was firm and rubbery to palpation. The mass felt more like an inflammatory than a neoplastic one. There were

numerous enlarged, anthracotic lymph nodes which bled more than usual on manipulation. These were located at the base of the fissure and in the region of the inferior pulmonary vein.

An adequate biopsy of the thickened pleura was taken for frozen section, and reported as nonspecific chronic inflammation by the surgical pathologist. A left lower lobe lobectomy was then performed. The appropriate vessels were ligated individually and silk technic was used throughout the operation. Two hundred thousand units of penicillin were instilled into the pleural cavity before closure of the chest wall. A fenestrated rubber tube was brought out through the ninth interspace in the mid axillary line and attached to a water-seal drainage apparatus. On return of the patient to the ward, a negative pressure of 6 centimeters of water was applied to the drainage tube.



FIG 3—Lower lobe of left lung showing the gray rubbery lobular mass occupying most of the lobe and reaching the pleura. Base of lung is to the left.

Postoperative Course Four hundred thousand units of penicillin were given intramuscularly to the patient daily for 8 days following the operation. Forty-eight hours after surgery, the drainage tube was removed. The wound healed well and the patient made an uneventful recovery. He was discharged on the 10th postoperative and 44th hospital day to be followed in the chest surgery and dermatology out-patient departments. On his most recent visit to the clinic 8 months later, he was completely asymptomatic except for infrequent episodes of slight discomfort in the anterior portion of his scar. His physical and roentgenographic findings were not remarkable, and his daily activities were as before the onset of his illness.

Pathology Gross The lower lobe of the left lung measured 15 x 6 x 6.5 cm., and the visceral pleura was everywhere smooth and glistening, except for a 7 x 5 cm area laterally which was thickened. In this region several small thin yellow plaques were found. The lobe was moderately heavier than usual. Palpation disclosed an irregularly nodular firm mass occupying most of the lobe and involving the pleura laterally. Only the apical region and basal area medially were unoccupied by the lesion.

GUMMA OF THE LUNG

On cut surfaces, (Fig 3) a wedge-shaped nodular mass 7 x 7 x 4 cm was seen in the dorso-lateral area near the base of the lobe. The apex of the mass directed toward the hilum and extended within 2 cm of the main stem of the lower lobe bronchus. The lesion was rubbery, firm and yellow-grey in color. It consisted of well circumscribed though coalescent nodules which extended to the pleura laterally. The pleura in this vicinity was thickened, firm and light grey, while elsewhere it was thin and pliable. On manipulation of the lobe a unique finding was noted when the mass partially separated from the adjacent tissue. The parenchyma in the dependent areas of the lobe was normally crepitant and air-containing, but at the hilum it was beefy red, congested and soft.



FIG 4—Low power photomicrograph of a small area of necrosis surrounded by a zone of fibrosis. Note exudative process in adjacent parenchyma.

Microscopic The grey elastic material was composed of coalescent nodules of necrotic material in which the ghosts of former cell structure could be identified frequently (Figs 4 and 5). The necrotic material was nowhere caseous in nature. It was a coagulative type of degeneration around which a dense wall of mature fibrous tissue had developed.

These connective tissue fibers were separated from one another by empty angular spaces, particularly in areas adjoining the necrotic tissue. There was considerable infiltration by chronic inflammatory cells of which large mononuclear phagocytes and plasma cells predominated. Many of the phagocytes had ingested a brown granular refractile pigment, while others were filled with a finely granular lipid substance. Occasional multinucleated giant cells were found. Perivascular cuffing of the small blood vessels was not a prominent feature and sclerosis of arteries and veins was not particularly remarkable. No organisms were seen in the Levaditi stained sections.

DISCUSSION

Only a few of the reported cases of pulmonary gummata have been verified by pathologic study. This is probably due to the rarity of the disease and also because it is difficult to demonstrate the specific spirochete on microscopic sections. Recently, the source material for reports has changed. Whereas the material for discussion in early periodicals was derived from autopsy findings, the papers on this subject during the past few years have concerned patients living with the disease. These recent articles, therefore, have discussed the clinical recognition of late acquired pulmonary syphilis without post mortem confirmation.



FIG 5—Medium power photomicrograph showing coagulative necrotic process eroding a small bronchus with an adjacent zone of fibrosis. No functional parenchyma is evident.

Gumma of the lung is twice as common in males as females, but the course of the disease in the latter is more fulminating.⁸ Karshner⁷ found that its peak of incidence is in the fourth decade of life, while Wohlhill¹⁵ noted that it is more common in the warmer climates. Excellent reviews of this subject have been written by Karshner,⁷ Carrera,¹ Howard⁶ and more recently by Lieu.⁹

The symptomatology of pulmonary gumma is like that of any chronic, low-grade infection of the lung. The onset is usually insidious and occurs late in the tertiary phase of lues. The lesion may be present without disturbing the host. Wilson¹⁴ has listed the symptoms in order of their frequency. Cough is

most often present and it is apparently persistent and extremely bothersome. Occasionally it is productive of small amounts of mucopurulent sputum. The patient may complain of dyspnea out of all proportion to the size of the lesion. Hemoptysis is relatively uncommon, but there may be either streaking of the sputum or copious bleeding. Fever and chills are usually absent. Chest pain may occur with extension of the disease process to the pleura. Some patients have complained of tightness in the chest.

The malady often simulates tuberculosis and both diseases may occur simultaneously. The gummas, however, usually cause a milder clinical course. Although gummas have been found in all lobes of the lungs, most authors agree that the right middle and both lower lobes are affected most commonly.

The physical findings are those of pulmonary consolidation. Dullness and rales may be noted depending on the location of the lesion. The presence of diminished breath sounds or bronchial breathing will depend on the patency of the bronchus or bronchi leading to the gumma. Pleural thickening will dampen the auscultatory findings, and contraction of the involved lung will distort the normal relationships of the adjacent intrathoracic structures.

Certain laboratory procedures may render corroborative evidence to the diagnosis of the disease in question. A positive blood Wassermann test will be of assistance, but if antiluetic therapy has been instituted, the serology may be negative. Pulmonary tuberculosis should be ruled out by repeated examinations of sputum concentrates or gastric washings for acid fast bacilli by competent technicians. The sputum should also be investigated for mycotic and non-specific spirochetal organisms. The intradermal reaction to old tuberculin is usually of little aid in the age group of these patients.

Very few cases of proven gumma of the lung have been studied roentgenographically.⁸ The criteria for diagnosis by this method are therefore not well established. On reviewing the reported cases it is evident that there are no characteristic roentgenographic features of the disease. It usually produces much the same picture as tuberculosis or other types of chronic pneumonitis with secondary fibrosis. Like tuberculosis, it crosses anatomic boundaries and may involve two or more pulmonary segments. If the lesion responds to medical therapy, there may be fibrosis and contraction of the affected parenchyma.

The more common diseases such as tuberculosis, neoplasm and chronic pneumonitis should be excluded before the diagnosis of pulmonary gumma is considered. A bronchoscopy should be performed to rule out a bronchogenic growth that might be seen. A luetic pulmonary lesion may cause a stricture of an involved bronchus,³ and there may be moderate endobronchial inflammation in the region of the gumma.¹¹ Hartung and Freedman⁷ emphasize that a positive, well documented history of syphilis should be obtained.

The therapeutic test has been used as an aid in diagnosis. Reduction in the size of a pulmonary lesion roentgenographically following the administration of antiluetic drugs has been considered to be supportive evidence that a gumma was being treated.^{7, 8} It is recognized, however, that this procedure

may not help in determining the presence of such a lesion¹⁴ If there is a reasonable suspicion of carcinoma, the duration of therapy should not be so prolonged that prompt surgical intervention is prevented

The pathology of pulmonary gumma has been discussed and reviewed by many authors^{1, 6, 12, 13} Summation of their findings includes a central area of coagulation necrosis with caseation surrounded by a varying degree of peripheral fibrosis which is infiltrated with lymphocytes, large mononuclear and plasma cells There is associated bronchial and vascular destruction Throughout the lesion, there is relative preservation of the elastic tissue elements

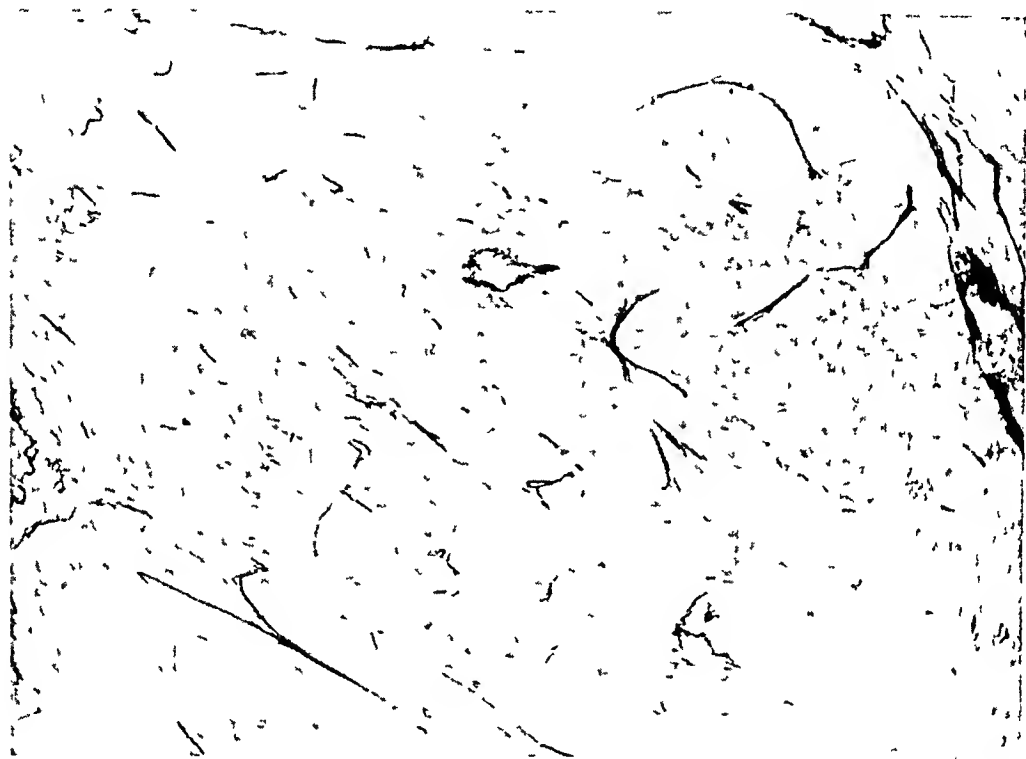


FIG 6—Low power photomicrograph of gummatous tissue stained with acid orcein Note persistence of elastic fibers in an otherwise degenerate material

Carrera¹ and others have emphasized that the demonstration of *spirocheta pallida* in the lesion by microscopy is the ultimate in diagnosis Howard⁶ has pointed out, however, that this has been accomplished rarely due to the inherent technical difficulties of such an examination Following the institution of antiluetic treatment, and with the present widespread use of penicillin for all types of pulmonary infection, it is evident that the search for spirochetes in pathologic sections will be even more fruitless

In the recent literature there have been numerous articles prescribing different types of medical therapy for luetic lesions of the lung^{8, 10, 14} The recommended regimes have met with varying success Diseased areas consisting primarily of inflammatory tissue may decrease markedly in size, leaving a small residual scar Unfortunately, many of the reported lesions which have shown dramatic roentgenographic response to medical treatment have never

been proven or examined pathologically. Mercurials, bismuth compounds and iodides have been prescribed for the initial treatment of pulmonary gumma either singly or together.¹⁴ After maximum response to one or all of these drugs has been obtained, an adequate course of an arsenical, usually mepharsen, is given. Favorable results with penicillin therapy of late gummatous syphilis elsewhere in the body have been reported. Dexter and Tucker² found this drug useful in a series of 21 cases. More recently, however, Hahn⁴ discussed a case of a penile gumma which did not respond to 4,800,000 units of penicillin, although it later cleared with the administration of bismuth and mepharsen.

It is difficult to determine the prognosis of patients with pulmonary gummas. Many of the case reports in the early literature were based on post mortem studies following death from pulmonary pyogenic infection. The more recently published cases have had more satisfactory clinical courses, but usually the lesions in question have not been studied histologically. If a suspected gumma of the lung shrinks roentgenographically to a small shadow following the medical treatment outlined above, the prognosis is probably good. Warthin¹³ has emphasized, however, that if a considerable amount of pulmonary fibrosis remains, the affected portion of lung yields readily to pyogenic infection. Suppurative bronchiectasis may result with the destruction of bronchial walls. Carrera¹ noted that terminal bronchopneumonia occurred in a high percentage of his cases. He thought that this was aggravated undoubtedly by the effect of syphilis on the myocardium. Repeated hemoptyses may be a serious hazard to patients with pulmonary gummas.

Extirpative pulmonary surgery is being performed today with an increasing degree of safety. The exploratory thoracotomy has become an accepted and helpful diagnostic procedure in many clinics. A gumma of the lung is an uncommon disease, but it may simulate the more prevalent pulmonary neoplasm,¹⁰ which, if operable, requires immediate surgical attention. A clinician is indeed in a precarious position if he makes the diagnosis of gumma when the signs and symptoms of a patient can be interpreted as carcinoma. By the same token, if there is not an immediate and significant favorable response of the lesion to antiluetic drugs, an exploratory thoracotomy should be performed. An experienced thoracic surgeon usually can differentiate at operation between an inflammatory and a neoplastic pulmonary lesion.

If a clinician encounters a pulmonary lesion which has all the presumptive criteria of a gumma, and if this lesion does not respond to medical treatment there is good reason to believe that permanent and serious parenchymal destruction has taken place. Unlike a gumma elsewhere in the body, such a disease in the lung will be exposed later to repeated secondary pyogenic infections, or it may be a potential source of hemorrhage. Since the disease usually occurs in the dependent portions of the lungs, subsequent bronchiectasis or suppurative disease may develop. It would seem logical therefore, that such a permanently damaged area of lung should be removed either by lobectomy or segmental lobectomy.

SUMMARY

The clinical features and pathology of gumma of the lung have been discussed. The case presented was first treated with penicillin and then by resection of the diseased lobe. A rationale for surgical treatment of pulmonary gumma is presented.

Grateful acknowledgment is made to Drs. Herbert C. Maier, A. Purdy Stout and Ross Golden for their assistance with the surgical, pathologic and roentgenographic aspects of this paper.

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CONGENITAL MICROCOLON A Case Report*

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CONGENITAL STENOSIS of the intestine is an uncommon condition, occurring about once in 20,000 births¹ It is generally agreed that most of these obstructions are due to intraluminal causes Davis and Poynter² noted that multiple sites of atresia are found in about 15 per cent of intestinal tracts so affected A complete survey of the literature dealing with congenital microcolon up to the year 1925 was published by Grieg³ He reported that even including atresia ani, congenital defects of the intestine are more frequently seen in the small bowel than in the colon The duodenum is the most common site of the lesion, the ileum is the second most usual area of involvement¹

Arnheim⁴ searched the literature to 1945 and learned of only 11 successful operations performed on jejunal and ileal atresia His publication provided the twelfth reported cure of infra-duodenal atresia, and proved to be the second such cure effected in the presence of complicating perforation and peritonitis In the past 35 years, more adequate roentgen-ray visualization⁵ and earlier surgical intervention^{6,8} have progressively and favorably influenced the prognosis for congenital anomalies of the gastro-intestinal tract

The case to be presented in this communication is of interest because a remnant of what appeared to be the intestinal end of the vitello-intestinal duct was clearly defined In addition, the characteristic clinical and surgical pictures of congenital stenosis of the ileum and colon were observed

CASE REPORT

J G, a white female of Jewish extraction, was delivered vaginally at term October 17, 1947, and appeared grossly normal at birth The birth weight was 7 pounds, 6 ounces The child was the second-born of healthy, young parents Family history was negative

Some 12 hours after birth the infant vomited several times, bringing up bile-tinged material, and her abdomen became progressively distended Nothing had been passed by rectum since birth A rectal catheter could be passed to a distance of only 5-7 cm The clinical diagnosis was confirmed by barium enema roentgenograms Blood examination and urinalysis provided normal findings

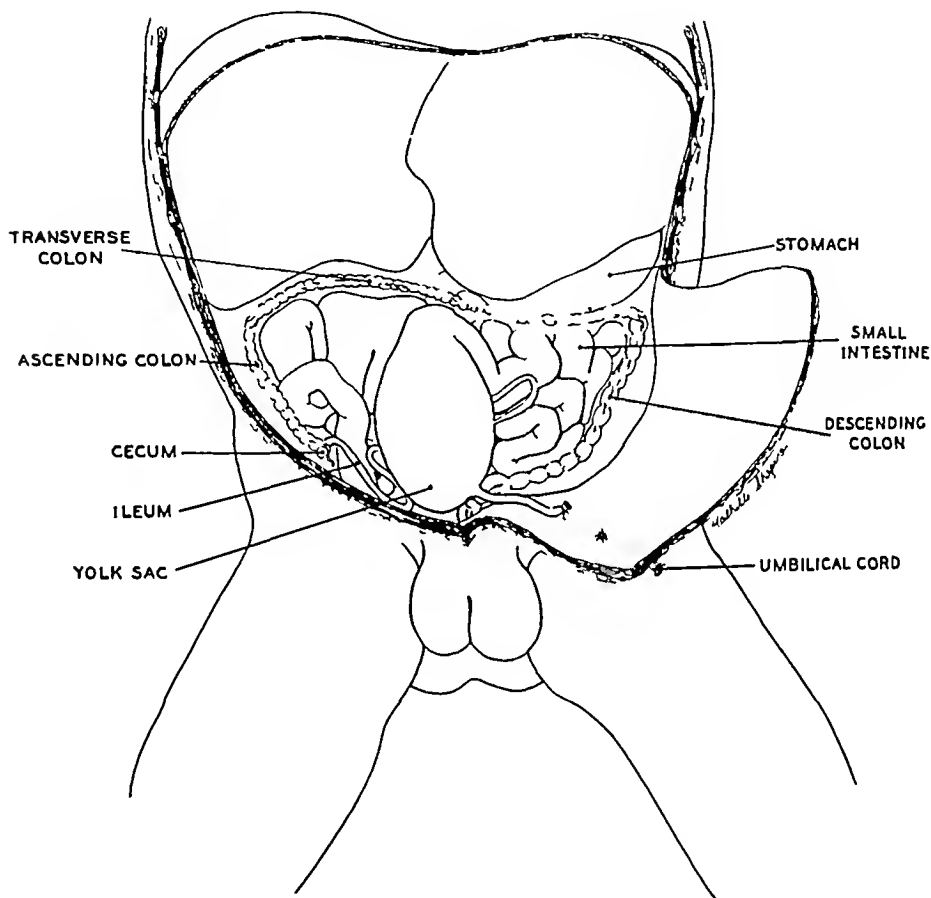
Under open drop ether anesthesia a laparotomy was done 24 hours after birth The entire colon and terminal ileum were found to be narrowed to about the thickness of a pencil, *i.e.*, about 1 cm in width, although a lumen was present throughout The small intestine was markedly distended, immediately proximal to the stenosed ileum it was dilated, in egg-shaped form, to approximately 5 cm in diameter A small duct, measuring 2.5 cm in length and 0.6 cm in width was present between the dilated ileum and the umbilicus This duct was ligated and severed (*cf* Figure 1) A side-to-side anastomosis was made between the dilated ileum and descending colon, at the splenic flexure

The infant was fed parenterally postoperatively and remained in good condition for 3 days Oral feedings were attempted at this time, but food so administered was promptly

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regurgitated. A Miller-Abbott tube was passed into the duodenum on the 5th postoperative day, but could not be advanced beyond this point. Oral feedings were again not retained. Nothing was passed per rectum. The patient lost weight and her clinical course moved steadily downhill.

On the 10th day of life a second laparotomy was performed under open drop ether anesthesia. At this time a catheter was passed rectally and it extended through the anastomosis and into the ileum. The ileal dilatation was observed to have decreased in size at this time. In handling the bowel a rent was accidentally made in the colon, and fecal material escaped into the peritoneal cavity.



CONGENITAL MICROCOLON AND
PORTION OF ILEUM WITH YOLK SAC

FIG 1

The postoperative course was stormy, there were frequent emeses, and repeated episodes of dyspnea and cyanosis supervened. The patient expired on her 18th day of life.

Autopsy Findings The body is that of a poorly nourished and poorly developed white female infant. The skin and sclerae are moderately jaundiced. Right rectus incision 8-9 cm. in length near the midline and a second, smaller incision to the left of the umbilicus containing a "cigarette" drain, which exude a slight quantity of purulent material.

Heart weighs 30 Gm (normal 19 Gm) but valvular and myocardial measurements are normal. Lungs are grossly normal except for a few atelectatic patches. Brain shows engorgement of blood vessels, but otherwise normal.

CONGENITAL MICROCOLON

The small intestine is greatly distended with air and fecal material, and is covered with a patchy, yellowish exudate. The loops are tightly adherent, and multiple adhesions to the abdominal wall and abdominal organs are present. The wall of the third part of the duodenum appears gangrenous (probably caused by the mercury bulb of the Miller-Abbott tube), and its external surface is covered with thick, yellowish exudate. The ileocolostomy appears secure and functional. The underdeveloped terminal ileum measures 16 cm to its cecal attachment, but is only 0.5 cm in width. The lumen is patent. The ascending and transverse colon appear normal in length, but measure only 0.6 cm in width. The descending and sigmoid colon measure 1.2 cm in width. A normal appearing rectum admits a finger easily. The mucosa of the entire intestinal tract is dark red.

The liver is enlarged and weighs 222 Gm (normal 123 Gm). Surface and cut sections appear icteric. Histologically, hepatic lobules are compressed and individual cells show atrophic changes.

Left adrenal is twice the size of the right, and has convex and bulging surfaces. Cut sections reveal a pale, necrotic, cheesy material distending the medulla and compressing the cortex.

The right kidney weighs 18.3 Gm (normal 15 Gm), and the left 19.5 Gm. The cut surfaces show diffuse congestion, but cortical and medullary boundaries are readily distinguishable. Histologically, the tubular epithelium displays marked degenerative changes.

Cultures of brain and heart blood exhibit bacterial contamination. *E. coli* hemolytica grown from peritoneal fluid.

Pathologic Diagnosis Peritonitis, ileocolostomy, hypoplasia and stenosis of terminal ileum, stenosis of entire colon, passive congestion of liver, cerebral congestion, jaundice.

COMMENTS

Not only the developmental mid-gut but also the caudal gut was involved in the congenital malformation observed in the above case. It appears highly improbable that faulty separation of the urogenital membrane in the process of definitive division of bladder and mesenteron occurred in this case, for such changes take place early in intrauterine life and anomalies of this origin involve lower segments of the colon. The duct observed here between ileum and umbilicus is more likely similar to a Meckel's diverticulum. Some error in reduction of the physiologic umbilical hernia may have participated in the production of this intestinal anomaly. Finally the time-honored explanation of failure of re-establishment of the bowel lumen after epithelial hyperplasia had occurred may be prudently invoked⁹ despite Grieg's³ contention that congenital microcolon represents physiological rather than anatomical error.¹⁰

Although a gesture was made surgically to anastomose the ileum to the descending colon it was appreciated, during the operation, that the colon was too narrow to be of physiologic value. This conjecture was borne out by the infant's death eight days after the second operation.

SUMMARY

A case is presented of congenital stenosis of the terminal ileum and entire colon in a white female infant. There was a fatal outcome in 18 days despite two surgical efforts to correct the defects. A rather unusual finding was the presence of a duct which joined a portion of widely dilated ileum to the

umbilicus Surgical cure was impossible by virtue of the extensive anatomical defects

The authors wish to acknowledge their thanks to Dr A Clarence Rice and Dr Adrian Racinos, pathologists at Children's Hospital, Washington, D C, for performing the autopsy and permitting use of their data in this paper

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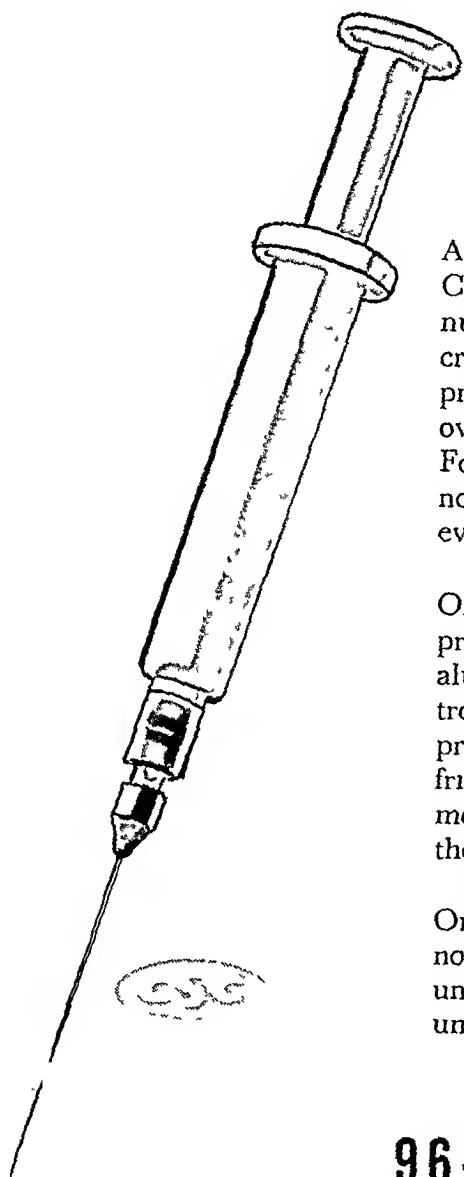
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MASSIVE HEMATEMESIS*

ANALYSIS OF 300 CONSECUTIVE CASES

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ONE COULD NOT JUSTIFIABLY UNDERTAKE to discuss the topic of massive hematemesis without reference to much in the vast library of reports on this subject but because of its extensiveness a thorough review cannot here be presented. Adequate reports have been made by Gray and Sharpe,¹ Zinninger,² Meulengracht,³ Heuer,⁴ Meyer,⁵ Eads,⁶ Allen and Benedict,⁷ Hinton,^{8, 9} Balfour,¹⁰ Jordan and Kiefer,¹¹ and a host of others. In seeking, however, to learn the best methods for management of this grave condition, one encounters a divergence of opinions among authors as to whether treatment should be medical or surgical and if the latter, how such cases are to be selected. Other problems in therapy include those concerning the advisability of using gastric siphonage, oral feeding, blood transfusions, and sedation.

In order to arrive at a better understanding of the principles of anatomy, physiology, and pathology involved and to correlate these principles with a plan of rational therapy, a study was undertaken at the St. Louis City Hospital.

In this study, 300 patients who had presented the symptoms of massive and severe hematemesis were selected. No patient was included in this study who had not vomited large quantities of gross blood and who did not show evidence of blood loss by shock or by severe anemia or by both. Thus, individuals who may have vomited as much as a cupful of blood, but who did not show evidence of shock or severe anemia, were omitted. A second portion of this project was begun early in 1946 and consisted of treatment of those patients presenting massive hematemesis according to a modified plan. The results in this series of 73 patients have also been determined.

CAUSES

In our series of 300 patients (Fig 1), chronic duodenal ulcer leads the list of causes, accounting for 171 patients or 57%. No diagnosis was made in four patients (1.3%). Acute gastritis was the underlying cause of massive hematemesis in 42 patients (14%) while chronic gastric ulcer accounted for 33 patients (11%). Ruptured esophageal varix occurred in 24 patients (8%) and

* Submitted for publication, December, 1948

chronic gastritis in 12 patients (4%) Gastric carcinoma was one of the rarer causes of massive hematemesis accounting for only four such cases (1.3%) Marginal ulcer occurred in four patients (1.3%), Curling ulcer in two patients (.6%) and carcinoma of the esophagus in three patients (1%) while trauma of a bullet wound was the cause in one patient (.3%)

SEX AND AGE INCIDENCE

Two hundred and forty-seven of the patients (82%) were males while only 53 patients (18%) were females (Fig 2) The incidence of massive hema-

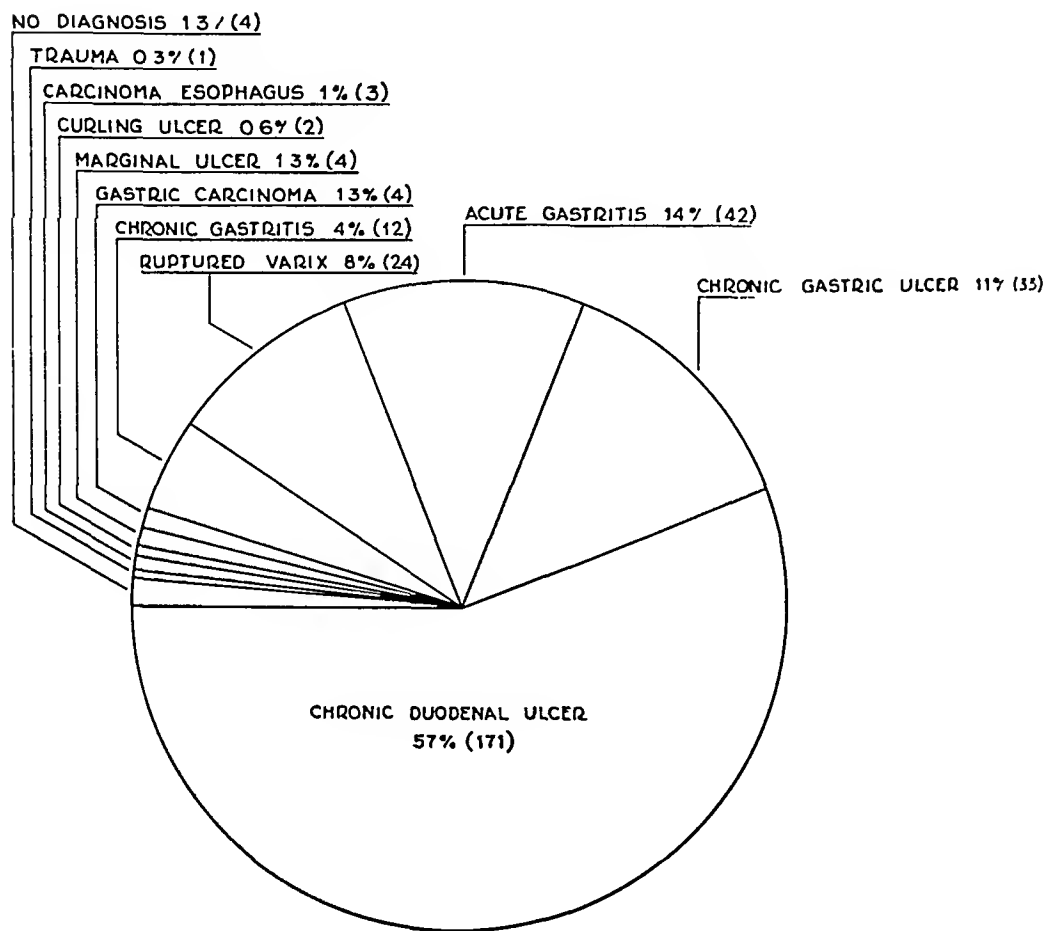
CAUSES OF MASSIVE HEMATEMESIS
IN 300 CASES

FIG. 1

temesis was greater between the fourth and eighth decades in both sexes, the highest incidence occurring in the sixth decade (23% of the males)

MORTALITY IN PATIENTS TREATED BY CUSTOMARY MEASURES

The overall mortality rate in 300 cases was 25% Consistent with observations and reports of others studying this subject, mortality rate was found to

increase in those who had reached or passed the fifth decade of life. Thus it was seen that among males, while in the fourth decade, only 10% died, 20% died in the fifth decade, 28% in the sixth, and 38% in the seventh (Fig 3). Certain pathologic lesions bore a higher mortality incidence than others (Fig 4). Thus of four patients who bled massively from carcinoma of the stomach, all died. The two patients with Curling ulcers, both died, and three patients of the four who presented marginal ulcers died. Of the 24 patients with ruptured esophageal varices, 71% died and in those patients who bled from carcinoma

SEX AND AGE INCIDENCE OF MASSIVE HEMATEMESIS IN 300 CASES

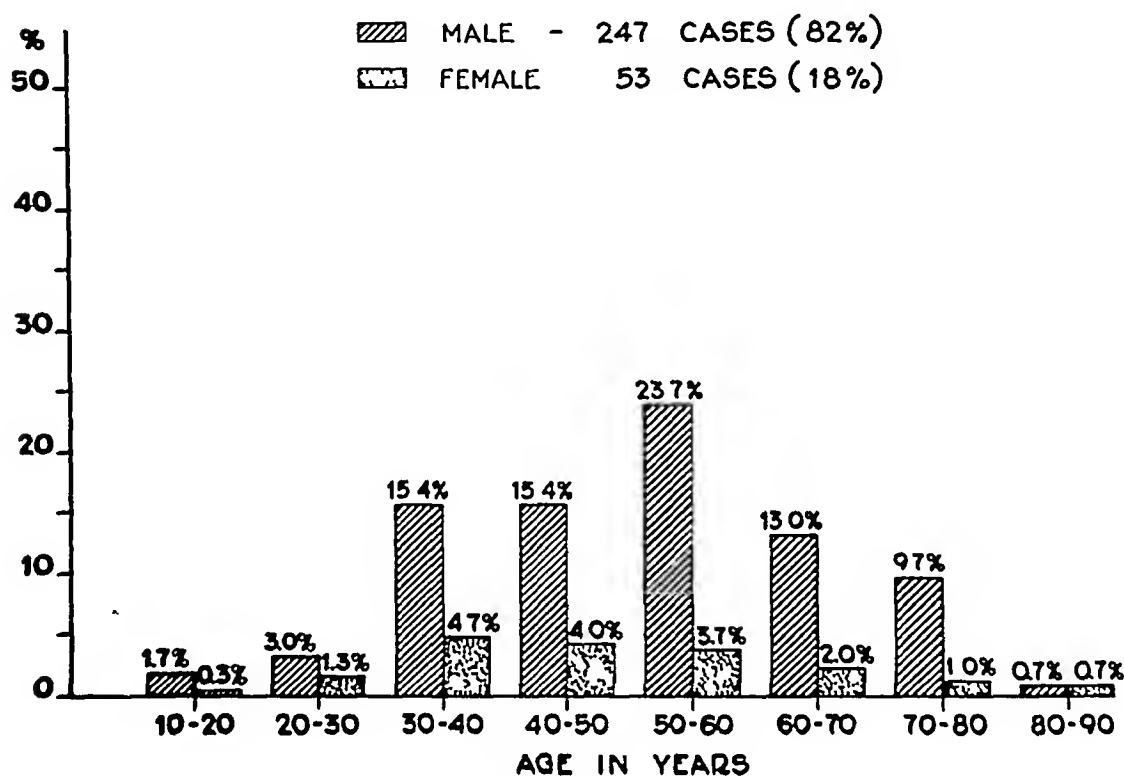


FIG 2

of the esophagus, 66% died. Of 33 chronic gastric ulcer patients, deaths ensued in 48%, while in those with chronic duodenal ulcer only 13% died. In patients who presented acute gastritis (42) only 12% died, and of those who presented chronic gastritis as the basis of massive hemorrhage (12) 9% died.

PATHOLOGY

Surgical or autopsy examination afforded opportunity for pathological examination in about 85% of those patients who died. Of particular interest and significance was the status of the eroded blood vessel. As is well known, the commonest vessels involved in such major upper intestinal hemorrhages are the branches of the right and left gastric and the pancreaticoduodenal

arteries and the esophageal veins. The size of vessels involved varied from large and prominent gastric arteries to those involved in multiple superficial gastric ulcers which could not positively be identified. In one instance erosion of a chronic gastric ulcer had extended into liver sinusoids.

Sections of arteries and veins involved were not obtained in all instances. However, in those who died with erosion of a large, easily demonstrable artery (usually in the base of a chronic ulcer) microscopic studies were usually performed. In nearly all of these sections there was seen and described a partial

MORTALITY BY AGE AND SEX IN 300 CASES OF MASSIVE HEMATEMESIS

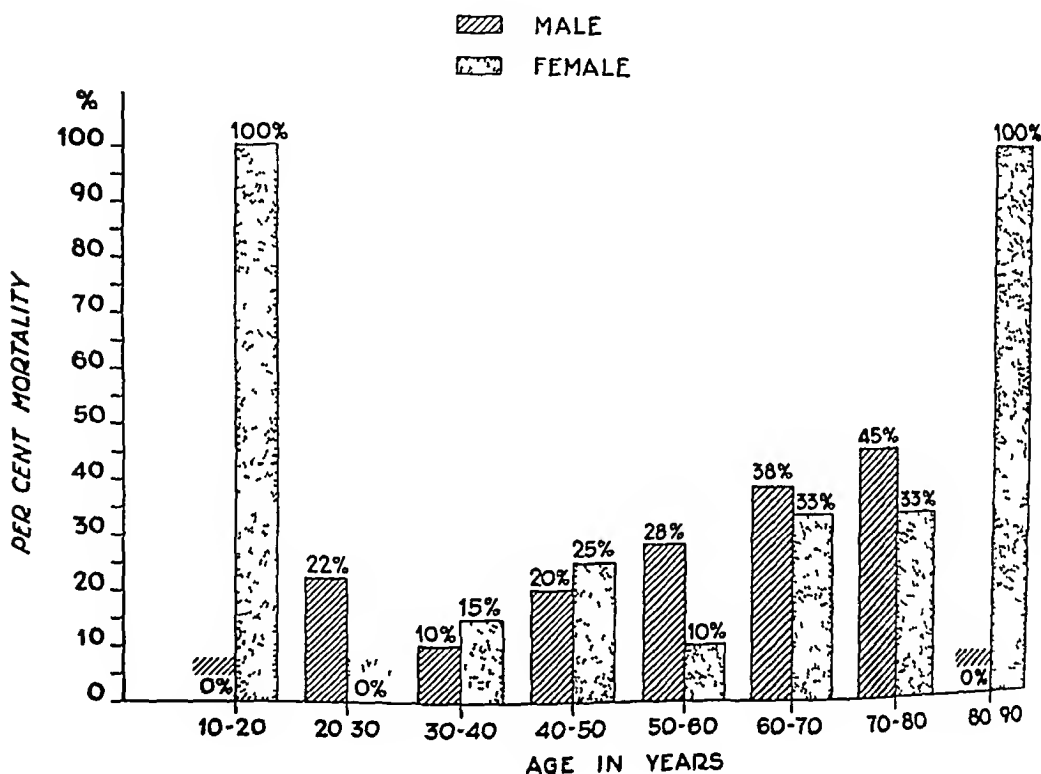


FIG 3

or complete block of the eroded wall by antemortem thrombus, and in these the stomach and duodenum contained little or no fresh blood. This demonstration of thrombus formation in even large eroded gastric arteries is of paramount importance in arriving at a rational plan of therapy. It is evident that many of these patients did not die, as has been commonly assumed, from acute exsanguination through a wide open artery. This misconception has led to recommendations that patients with arteriosclerosis and chronic ulcers should be subjected more promptly to operative closure of the bleeding point. It would rather appear on the basis of pathologic studies that just the contrary is true, for thrombus has often already formed prior to the time of death and such a

MASSIVE HEMATEMESIS

death, therefore, must be attributed not to continued acute hemorrhage but rather to the complications of diminished blood volume (shock, cardiac failure, anemia, pneumonia, *etc*) produced after the hemorrhage had ceased. This fact is confirmed by the clinical course of patients who died. They did not die in a matter of minutes or hours (with one exception) as would be expected from a persistent fulminant hemorrhage, but died from two days to three weeks after the onset of bleeding. Of the 75 patients who died, 71 of them did not receive even a moderate fraction of blood which would have been required to replace the amount lost.

On this evidence then one must logically reason that therapy should primarily be directed not toward surgical closure of the injured vessel which natural processes often will close spontaneously, but toward support of the depleted blood volume.

PHYSIOLOGY

The body response to massive blood loss is well known. In an attempt to supply vital centers with the remaining blood volume there is a generalized vasoconstriction, an increased rate of heart action, and absorption of tissue fluids into the general circulation. If inadequate blood volume continues, anoxia with its irreversible tissue damage ensues. In view of the universal acceptance of this well-established fact, it is surprising to find recommendations still made that in such a situation blood should not be used or if used, should be used sparingly. The theory that restoring blood pressure risks "blowing out" a forming thrombus has no scientific substantiation while on the other hand, no one has yet been able to improve on shock-prevention as the best shock-therapy. To wait for a fall of blood pressure to 80 or 100 mm of mercury before administering a "small transfusion" as is often recommended is a direct contradiction of sound physiologic principles.

BLOOD REPLACEMENT PLAN

If these pathologic facts and physiologic principles are correct, the optimal choice of treatment in massive hematemesis should be essentially replacement of as much blood as has been lost as promptly as possible until thrombus formation has sealed the eroded vessel or vessels. In testing these principles during the past two years, 73 patients were treated by adequate and prompt blood replacement. The distribution of these 73 patients by sex and age corresponds closely to that of the previous group studied. There were for example 51 of these 73 patients who had reached or passed the fifth decade of life, and there were eight of these who had reached or passed the eighth decade of life. Operative interference during active bleeding was not undertaken in any of these cases. Feedings were usually administered, and the type of feeding varied between the Meulengracht diet, the Sippy diet, liquid diet, and protein-dextrin-maltose ("pre-digested") liquids. As should be anticipated, the difference in mortality rate was striking (Fig 5). Only 4% of this group of 73 patients died as compared to 25% of the 300 treated by various methods.

In further analyzing this difference in mortality, it is clear that the single most important factor in minimizing death has been that of adequate blood replacement. It is highly doubtful if this policy could be routinely used in an institution which does not have a blood bank facility. The total quantity of blood required by many of these patients is enormous as judged by transfusion standards of a decade ago. Often patients who had lost large quantities of blood and who were still bleeding when admitted to the hospital received as much as three and four liters of blood during the first 24-hour hospital period. The frequent use of intravenous saline solution should be condemned as it does nothing toward re-establishing blood volume, and encourages pulmonary edema. The fluid of most value to be used while blood is being cross-matched

MORTALITY (25%)
75 DEATHS IN 300 CASES

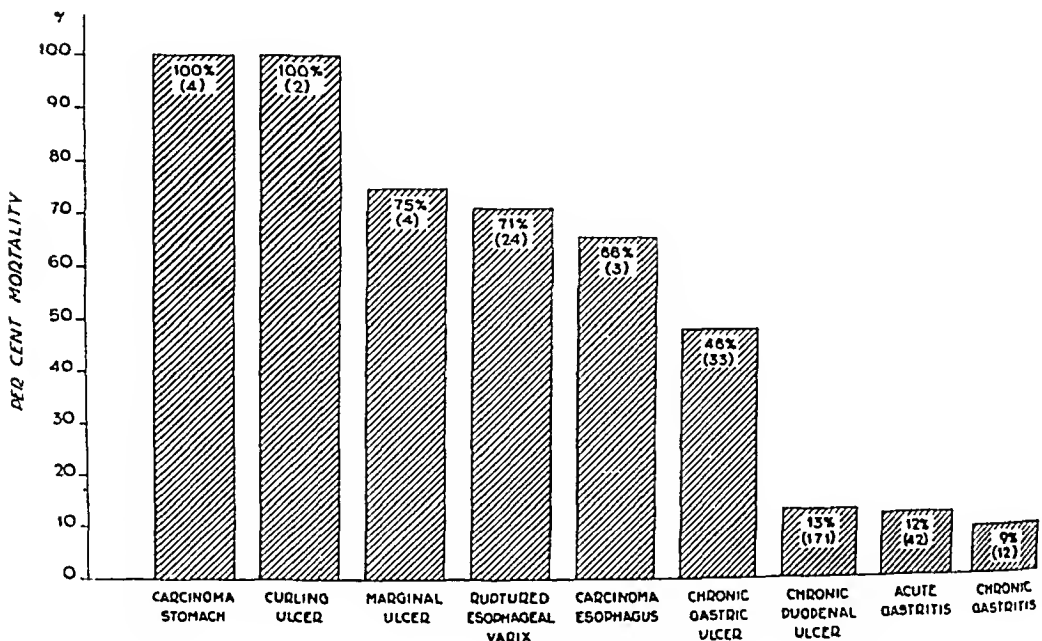


FIG 4

is plasma. Another essential for enforcing adequate blood replacement is the readily available facility for rapid determination of blood requirements. The need for blood cannot properly be determined by a patient's general appearance, pulse, or blood pressure. The older methods of blood study such as blood count and hematocrit are either undependable or too *time consuming* to be of value in these cases. The most desirable method for accurately following blood volume changes is the copper sulfate falling drop method.¹² The device for this simple procedure has been set up on the hospital divisions and in the matter of a few minutes with only a few drops of blood, the initiated house officer is able to discover the specific gravities of blood and plasma, the hemoglobin, and the hematocrit.

In addition to blood volume replenishment, several other factors have been given special attention

- 1) Gastric siphonage
- 2) Diet and antacid therapy
- 3) Sedation
- 4) Surgery
- 5) Early differential diagnosis

1) *Gastric Siphonage* The insertion of a Levine tube via the esophagus into the stomach was seen to produce fatal hemorrhage in two patients. It was instrumental in provoking increased hemorrhage in several others. Ice water for lavaging was used in the two cases of fatality, and one of these

1946 - 1947
(ADEQUATE BLOOD REPLACEMENT)

73 PATIENTS - 3 DEATHS
(4% MORTALITY)

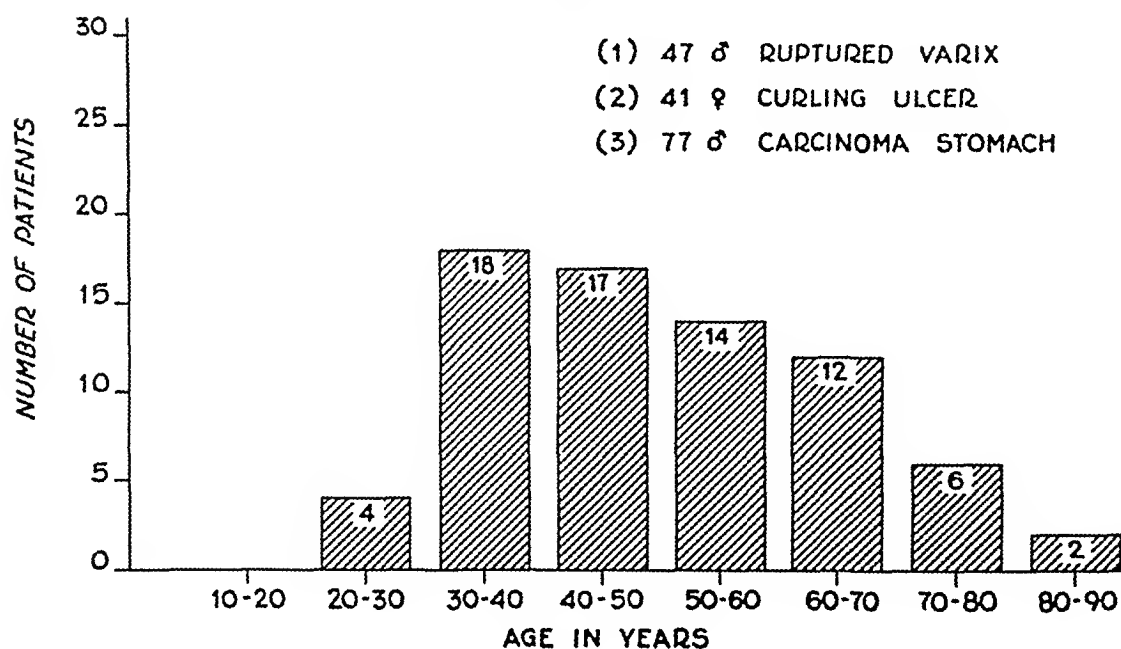


FIG 5

patients expired while the process was being carried out. The danger of traumatizing a varix or ulcer should interdict use of the tube unless there is definite gastric distention and nausea.

2) *Diet and Antacid Therapy* The question as to whether feeding should or should not be employed has long been debated. Meulengracht has reported favorably on feeding pureed diets although a large proportion of his ulcer patients presented only minor bleeding. In the light of current knowledge that most of these patients have a deficit of protein and vitamin which impedes

tissue repair, it becomes imperative that they receive large amounts of readily assimilable protein, carbohydrate, and vitamin. The most satisfactory method for administering these essentials we have found has been oral ingestion of 200 cc every two hours of the following preparation

Predigested protein powder (polypeptide)	150 Gm
Dextrin-maltose	300 Gm
Vitamin C (cevitamic acid)	1 Gm
Liquid multiple vitamin	1 cc*
Water q s	2400 cc

This preparation is well tolerated with rare exception and serves not only the purpose of supplying greatly needed nutriment but also produces symptomatic relief of ulcer pain. This is apparently accomplished through the protein antacid effect which is much more effective in degree and in duration than the more commonly employed antacid powders. This same preparation has been highly satisfactory in relieving severe ulcer pain of impending perforations. The polypeptide component is used rather than amino acids since it is palatable.

3) *Sedation* The most generally adopted plan for sedation in the past has been that of administering morphine or barbiturate as needed. In practice this usually degenerates to a matter of a sedative being finally given after the patient has repeatedly complained to the nurse of restlessness, fear, or pain. The numerous psychogenic impulses attendant upon massive hemorrhage and nausea have appeared often to provoke further active bleeding and it has, therefore, been our policy to relieve these patients totally of their adverse stimuli. This has been accomplished by administering a single initial dose of morphine followed by hypodermic injections of two grains of sodium phenobarbital every two hours as needed to keep the patient drowsy. We have considered the patient properly sedated when it is necessary physically to arouse him in order to obtain replies to questions. The danger of oversedation must, of course, be carefully avoided.

4) *Surgery* The major disadvantages to surgical procedure during active bleeding are: a) Patients are in poor condition from blood loss and while bleeding is active they may be expected to become worse.

b) Nutritional deficiencies of a chronic nature must be anticipated in patients whose ulcers are active enough to have produced erosions of major vessels. Operations undertaken before these deficiencies have been corrected must result poorly in many cases.

c) The nature and location of the ulcerative lesion cannot safely or accurately be determined early in the course of hemorrhage and routine operative approach with its risk cannot be serviceable or successful enough in treating all causes of massive hemorrhage to justify its use. As pointed out by Stone¹⁴ such an operation may still fail to discover or relieve the trouble.

d) Finally, the ultimate test of value, that of clinical results in the non-

* Any liquid vitamin which contains the daily requirements should suffice. Upjohn's "Zymadrops" has become our material of choice.

surgical treatment of massive hemorrhage speaks unequivocally against operative interference. Prior to our initiation of this non-operative plan of therapy, ten patients had been operated upon late but while still bleeding and death ensued in 90%.

An interesting study in this regard is being conducted by Stewart¹³ *et al*. They are combining massive blood replacement and exploratory laparotomy within the first 24 hours of hospitalization. Their results in such treatment of 19 patients have been accompanied by four deaths representing a mortality of 21% which may improve as the series of cases enlarges but which we doubt will ever compare favorably to active and complete non-surgical management.

A word should be said about that small group of patients who continue bleeding for seven to ten days or who begin bleeding again after apparent control. While the urge to intervene is great, the wisdom of persisting in the plan as set forth has been demonstrated conclusively in this series in that all patients finally ceased bleeding and were improved to the point that surgery could be undertaken without great risk. On the other hand, the inadvisability of operating on this type of patient is forcibly demonstrated by our extremely poor results of nine deaths in those ten patients so treated prior to our adopting the non-surgical plan.

5) *Early Differential Diagnosis*. The patient with active or recent major intestinal hemorrhage should not be subjected to enthusiastic diagnostic routines. Hemorrhage should be treated only symptomatically until controlled and then the matter of diagnosis may be pursued without the great danger of re-precipitating or exaggerating hemorrhage. In our own series of patients we have seen major hemorrhages re-started by barium studies and gastric analyses. The information so obtained rarely if ever alters the prescribed course of therapy early in the condition and so it becomes a matter of accomplishing an earlier diagnosis solely for the purpose of the record at the expense of increased mortality. It requires seven to ten days for moderately firm fibroblastic tissue reaction to form in an organizing thrombus and this picture should be borne in mind by the gastroscopist and fluoroscopist lest irreparable harm be done.

SUMMARY

Some of the results from a study of 300 patients with severe, massive hematemesis have been presented. The results of 73 patients treated by a massive blood replacement plan have also been presented. Mortality by this latter plan has been reduced to 4%. There was no death from chronic peptic ulcer, the commonest cause of massive hematemesis.

The following plan is, therefore, recommended for treatment of massive hematemesis during the actively bleeding stage.

- 1) Careful determination of blood needs by the copper sulfate falling drop method repeated frequently
- 2) Complete restoration of blood as promptly as possible

- 3) Oral administration of predigested protein-carbohydrate-vitamin mixture
- 4) Adequate, continuous sedation

The following procedures have been found to increase mortality during the actively bleeding stage

- 1) Surgery
- 2) Indwelling stomach tube with constant suction
- 3) Gastric lavage
- 4) Active gastric diagnostic studies

The problems in management of these patients after the active hemorrhage stage has passed have not been the province of discussion at this time, but instead, emphasis has been placed on the principles and factors of importance in the management during the stage of active hemorrhage. Following the control of hemorrhage and the restoration of nutrient and blood essentials, the advisability of elective surgical intervention may more easily be determined.

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THE MANAGEMENT OF BLEEDING DUODENAL ULCERS*†

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THE SURGEON FACES FEW THERAPEUTIC problems that are more perplexing than the management of a patient who has had a sudden, massive hemorrhage from a duodenal ulcer. It is a question of which course of action is most likely to lead to recovery, and when confronted with the individual case, statistics do not provide the answer. Reports have been difficult to interpret as authors have not always set down clearly their criteria for placing a patient in the severe hemorrhage group.

Recent publications by Heuer,¹ Gordon-Taylor,² and Hinton,³ indicate that the present mortality rate without operation varies between 8 and 12 per cent in the United States and England, while Meulengracht⁴ reports the death rate in Denmark, under his free feeding regime, as 2.5 per cent. These results are a distinct improvement over the mortality rate of 15 to 74 per cent reported much earlier by Gordon-Taylor,⁵ Finstere,⁶ Chiesman,⁷ Allen,⁸ and others. The improvement in the nonoperative group appears to be due largely to the more generous use of blood transfusions.

Surgeons quite naturally have been interested in a direct attempt to stop bleeding by ligation of the bleeding vessel or vessels. This objective, as a rule, has been accomplished by gastric resection with excision of the ulcer and ligation of the vessels adjacent to the ulcer. In the past such a major procedure in a seriously ill patient usually carried a high mortality although Gordon-Taylor⁹ in 1939 reported a series of 18 cases operated upon within 24 hours of the onset of bleeding with only one death, a mortality rate of 5 per cent, and Heuer¹ in 1946 reported a 10 per cent mortality in 21 cases operated upon at the New York Hospital. According to the same authors, operations performed 48 hours or longer after erosion of a large vessel resulted in a 50 to 70 per cent mortality rate.

These figures support the repeatedly stressed advice that, if surgery is to be carried out with a low mortality the decision to operate must be made early. This decision is frequently a difficult one because during the first 48 hours there is no certain way by which the fatal type of hemorrhage can be differentiated from bleeding which will stop with nonoperative measures. Continuous recurrent, or sudden massive hemorrhage under a strict medical regime generally are accepted as the prime requisites for operation during the bleeding stage.

Mikulicz¹⁰ reviewed the problem of treating bleeding duodenal ulcers 51

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years ago and came to the conclusion, as did Kronlein,¹¹ about 10 years later, that operation during the phase of active bleeding was extremely hazardous and that the patients stood a much better chance of survival if subjected to a conservative regimen.

It was Finsterer,^{12, 13} who drew attention probably more emphatically than any other surgeon to the high mortality rate which followed late intervention in bleeding duodenal ulcers. After watching several deaths in young persons, he started his policy of operating at the end of 48 hours if the hemorrhage had not stopped. In his estimation, the third day was the critical period after which surgical intervention resulted in a disproportionately high mortality. In 1918 he started the first of a long series of contributions advocating early intervention with gastric resection and pyloric exclusion. In 1933 he⁶ reported 46 cases operated upon early (within 48 hours) with a mortality rate of 4.3 per cent and a group of 55 patients operated upon after this interval with a mortality rate of 32.7 per cent. His enthusiasm for early intervention has been shared by Allen and Benedict¹⁴ in so far as it pertained to the older age group.

While blood transfusions were used during these years, the blood was not administered in the generous amounts that were found beneficial in treating traumatic hemorrhage encountered in World War II. With adequate blood replacement, which is possible with a reliable blood bank, both the internist and the surgeon are allowed more time in which to plan a patient's therapeutic course and there is reason to believe that this factor alone will result in improved mortality figures for both the operative and nonoperative cases.

It is interesting to note that Gordon-Taylor,² who was one of Finsterer's early adherents, recently has changed his views about the urgency of immediate surgery. After making an intensive study of the disease in Great Britain, he has been impressed by the improvement in nonoperative measures now being employed and in his latest article arrives at the conclusion that "while Finsterer's third day may possibly be a critical period for operation the successful intervention at a later date in patients suffering from bleeding belie the universality of the dictum."

We have reviewed the records of 177 patients with severe bleeding from duodenal ulcers. The diagnosis was established by roentgenography, operation, or, in the fatal cases, by autopsy. The criteria of severe bleeding were a drop in hemoglobin to 65 per cent or less and a reduction in red cells to 3,500,000, or less. One hundred and eight of these patients had a hemoglobin of less than 50 per cent and a red count of less than 2,500,000.

In this series of 177 cases (Table I) there was a total of 11 deaths, a mortality rate of 6.2 per cent. One hundred and sixty-five patients were treated by nonoperative measures with seven fatalities, a mortality rate of 4.2 per cent. Twelve patients did not show a satisfactory response to conservative treatment and were operated upon while actively bleeding. All were operated upon in the late period, that is after more than 48 hours of rapid blood loss, and four died, a mortality rate of 33.3 per cent.

BLEEDING DUODENAL ULCERS

There were 93 patients under 50 years of age (Table II) Nine were treated by operation with three deaths, a mortality of 33.3 per cent, but there were no deaths in the group of 84 patients treated without operation

There were 84 patients over 50 years old (Table III) Three were treated by operation with one death, a mortality of 33.3 per cent Eighty-one were

TABLE I—*Bleeding Duodenal Ulcers*

Treatment	Number of Patients	Deaths	Mortality %
Non-operative	165	7	4.2
Operative	12	4	33.3
Total	177	11	6.2

TABLE II—*Bleeding Duodenal Ulcers*

Treatment	Under Age 50 Number of Patients	Deaths	Mortality %
Non-operative	84	0	0.0
Operative	9	3	33.3
Total	93	3	3.2

treated by nonoperative measures and seven of these died, a mortality of 8.6 per cent Since there were no deaths among the patients under 50 years of age who were treated without operation, it would appear that age is a factor of some importance in estimating the chance of survival of a patient under conservative treatment

TABLE III—*Bleeding Duodenal Ulcers*

Treatment	Over Age 50 Number of Patients	Deaths	Mortality %
Non-operative	81	7	8.6
Operative	3	1	33.3
Total	84	8	9.5

Of the patients beyond 50 years of age who died of hemorrhage, the advent of the bleeding phase of the ulcer generally was accompanied by additional pathologic conditions which contributed materially to the ultimate demise Arteriosclerosis appeared to be one of the most important contributory causes of death (Table IV)

A summary of the operative deaths is shown in Table V Two of the four operative deaths appear to have been caused by pulmonary complications while the other two deaths were due to failure to control the bleeding

by operation, in one case a transduodenal suture of the bleeding ulcer was attempted and in the other the ulcer was not excised at the time of the gastric resection and continued to bleed

TABLE IV—*Bleeding Duodenal Ulcers*
Analysis of Non-operative Deaths

Sex	Age	Lowest		Trans- fusions Whole Blood	Duration of Life After Bleeding Started	Comments
		HB	R B C			
Male	60	38%	2 3 M	None	11 hours	Admitted to G U service with hydronephrosis luteal aortitis coronary sclerosis
Male	73	45%	2 2 M	1000 cc	21 days	Slow blood loss Bundle branch block Senile dementia
Male	80	32%	2 1 M	500 cc	13 hours	Cirrhosis of liver Coronary sclerosis Diabetes Mellitus Senility
Male	60	49%	2 5 M	500 cc	11 hours	Paresis cerebrospinal syphilis Death from cerebral embolus
Male	63	18%	1 0 M	6200 cc	4 days	Posterior ulcer which did not penetrate into pancreas
Male	65	46%	2 1 M	1000 cc	3 days	Sudden death without shock Large substernal mass
Female	50	41%	2 3 M	3600 cc	12 days	Marked arteriosclerosis Died of cerebral hemor- rhage with HB of 72%

TABLE V—*Bleeding Duodenal Ulcers*

Sex	Age	Lowest		Analysis of Operative Deaths		Trans- fusions Whole Blood	Type of Operation	Comment
		HB	R B C	Previous Bleeding Episodes	Pre- operative Bleeding			
Male	36	45%	2 6 M	1	3 days	2750 cc	Gastric resection	Death 48 hours after operation with temperature of 107 and pulmonary consolidation
Male	38	54%	3 1 M	1	11 days	2000 cc	Gastric resection	Hiccoughs pneumonia on 14th postoperative day
Male	29	37%	2 0 M	3	4 days	2800 cc	Trans- duodenal suture	Death from hemorrhage 10th postoperative day
Male	67	42%	2 1 M	4	4 days	5500 cc	Gastric resection	Ulcer not removed Death from hemorrhage on 3rd po topera- tive day

The results in patients under 50 years, not subjected to operation, are impressive. Although it is unlikely that the mortality rate for this group could be kept at zero indefinitely we do agree with Allen¹⁵ and Wangenstein¹⁶ that the death rate should be under 5 per cent and probably well below this

Allen¹⁵ in his study of this problem has come to the conclusion that if surgery is to be undertaken in patients under 50 years of age it is difficult to visualize a mortality rate of less than 5 per cent, if an adequate operation is carried out. He defines as adequate some type of gastric resection which controls the blood supply of the gastroduodenal, right gastric and gastroepiploic arteries.

The problem of surgical intervention in the patient who has survived a severe hemorrhage is a difficult one. Hinton¹⁷ has shown that a high percentage of patients suffer only one severe hemorrhage and Lahey¹⁸ in a study made at his clinic found that of 100 patients treated by a high gastric resection with removal of the duodenal ulcer, 28 bled at some time subsequent to the operation. Five of these patients were proven to have jejunal ulcers.

SUMMARY AND CONCLUSIONS

- 1 The total mortality in a group of 177 consecutive patients suffering moderate to severe hemorrhage, from duodenal ulcer, was 6.2 per cent.
- 2 Nonoperative treatment of 165 patients resulted in 7 deaths, a mortality of 4.2 per cent.
- 3 Operative treatment of 12 patients suffering from severe and uncontrolled hemorrhage was followed by 4 deaths, a mortality of 33.3 per cent.
- 4 Operation apparently saved the lives of four patients in this series but at the same time it appears probable that some of the patients subjected to operation might have survived without surgical intervention.
- 5 The occasional indications for surgical treatment of bleeding duodenal ulcer are limited with few exceptions to patients over 50 years of age.

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THE EFFECT OF INJURY ON WOUND HEALING*

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THE NATURE of the initial force in wound healing still remains an unsolved problem. In 1892 Wiesner²¹ suggested that injured cells release substances which stimulate normal cells to multiply, and in 1921 Haberlandt¹¹ proved that damaged *plant cells* release a substance which promotes proliferation of other living cells of the same kind. He called this substance a wound hormone. In 1912 Carrel¹ discovered that embryonic tissue juices stimulate epithelial cells and fibroblasts *in vitro* to intense proliferation.

Fischer¹⁰ found in 1930 that *tissue cultures in vitro* grew faster after being traumatized. He believed that a phospho-protein or a nucleo-protein was responsible for this effect. It has not as yet been possible to decide, however, whether wound healing in living organisms is initiated and promoted in the same manner. The hypothesis lay close at hand that if such substances were produced by wounds in living organisms they could be released into the circulation and promote healing in other parts of the body. Several investigators, among them Loin-Epstein,¹⁸ 1927, and Frankel,¹² 1928, reported observations to support this hypothesis, but it was not until 1941 that Young, Fisher and Young²⁴ gave evidence that was statistically satisfactory.

They made superficial skin defects on the backs of rabbits, measured the healing rate planimetrically, and found that if secondary wounds were inflicted 10–12 days after primary wounds, the former healed more rapidly than the latter. At the same time the present author was studying how the healing of sutured cutaneous incisions was affected by different local and systemic factors. For mensuration of the healing process the tensile strength (T S) of the wounds was tested by the method originally described by Chlumsky,⁴ 1899, and further developed by Harvey¹⁴ and Howes and Harvey,¹⁵ 1930. The results of this work were reported in 1944.¹⁹ Among the various control series there was one in which symmetrical wounds were made with an interval of 7–13 days between them. It was found that the rate of healing of the secondary wounds as expressed by their T S on the 5th to 7th day was greater than that of the primary wounds. This finding supported the results obtained by Young *et al* and showed that in sutured incised wounds the fibroplasia as expressed by the returning T S is accelerated if the organism is already engaged in a healing process.

The following experimental series demonstrates this healing-promoting effect. For technical details and statistical considerations the reader is referred to the author's previous work.¹⁹ In a series including 11 rabbits two

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incisions, one in front of the other, were made on the back of each. After exactly five days the wounds were excised and their tensile strength (T S) measured using a tensiometer (first observation T S Gm). Fifteen days after the first wounds had been made two new incisions were made on the other side of the body, strictly symmetrical with the first ones. These were also excised on the fifth day and measured in the same way (second observation T S Gm). The values obtained representing the T S in grams are shown in the table.

TABLE I—Wound age 5 days, interval 15 days

No	First Observation T S Gm	Second Observation T S Gm	Relative Difference Second Minus First Observation	Mean
9	196	365	60	54
	260	423	48	
10	358	453	25	30
	246	360	38	
11	266	337	24	11
	258	252	-2	
12	208	357	52	81
	142	492	110	
15	367	634	53	50
	311	510	48	
16	420	810	63	56
	406	668	49	
27	292	355	19	-10
	412	277	-39	
29	240	454	62	79
	206	590	96	
30	345	570	49	28
	308	333	8	
35	495	379	-27	22
	200	416	70	
36	187	203	8	8
	(103)	(450)		
$n = 11 \quad m = 37.2 \pm 8.84 \quad \sigma = 29.3 \quad M = 45.7$				

The relative difference given for each pair is the difference between the second and the first observation in per cent of their average. The mean (m) from the whole series is an expression of the difference between the second and first observation and has been used for examination of statistical significance.

cance (A modification of m written $M = \frac{100m}{100 - \frac{m}{2}}$ has a more obvious meaning it expresses in per cent the increase or decrease in T S of the second observation in comparison with the first)

The results are shown in the diagram (Fig 1), in which the mean of the T S of the two primary wounds is represented by a white rectangle. It has

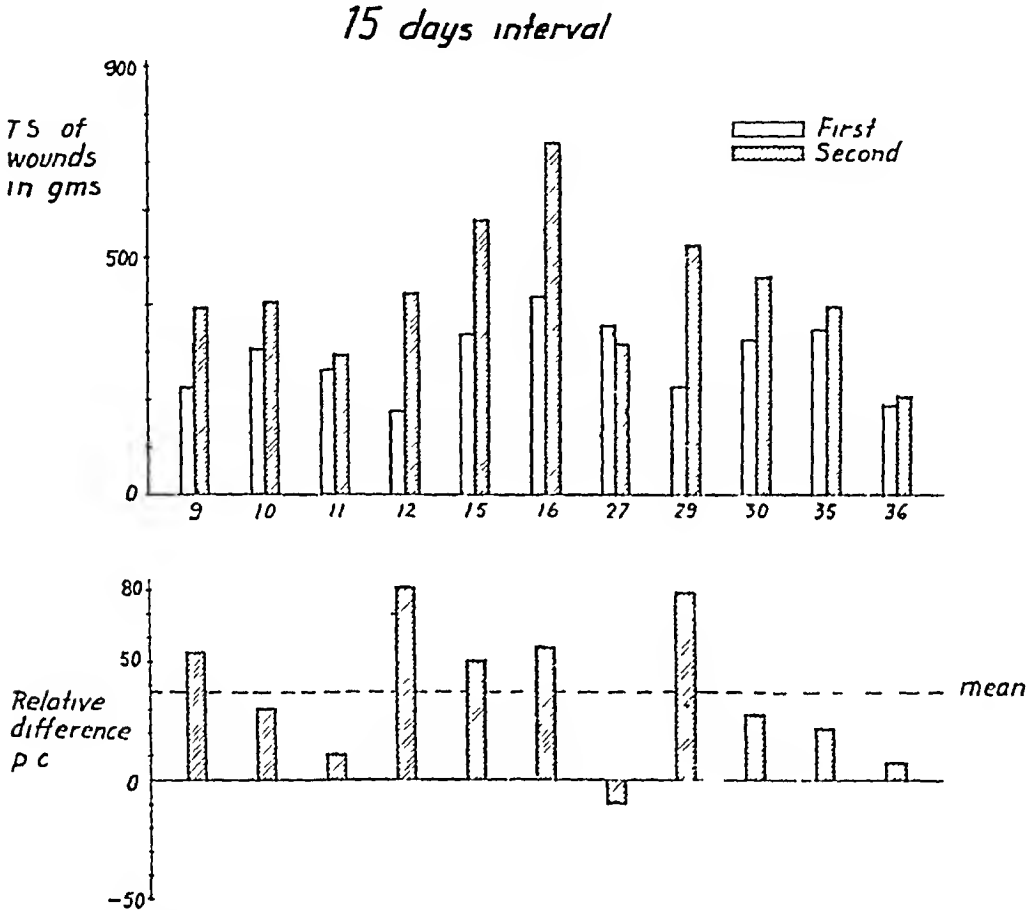


FIG 1—The upper diagram shows the T S of the primary wounds as white rectangles and the T S of the secondary wounds as shaded rectangles. The lower diagram shows the relative difference between the T S of the secondary and the primary wounds. The interval between the infliction of the primary and the secondary wound was 15 days and the T S was measured on the 5th day throughout.

been put next to a shaded rectangle representing the same values for the secondary wounds. The mean relative difference in per cent has been represented on the lower graph. When it is positive it means that the secondary wounds were stronger than the primary ones, when it is negative they were weaker.

It may be seen from Table I and Figure 1, that the secondary wounds were stronger than the primary wounds in all instances but one, and that the mean difference is $37.2 \pm 8.84\%$ which is a statistically significant value.

The cause of this healing-promoting effect is not known. It is not likely that it is due to local influence, as the wounds were made far apart on opposite

sides of the body—that is to say, in sections with separate circulation (The secondary wounds might heal under somewhat increased tension after the primary wounds have been excised but the difference, if any, is probably insignificant Weiss²² has shown that tension has a directive effect on tissue growth *in vitro*)

If the cause is a systemic change there are several possible explanations. The oldest is the "wound hormone" concept. As mentioned above, such substances have been shown to be released by injury to plants and to tissue cultures *in vitro*. For more information the reader is referred to an article by Davidson,⁶ a monograph by Fischer¹¹ and articles by Cook and Fardon *et al.*⁷ and by Loofbourov and associates.¹⁷ Through the investigations of the latter some knowledge has been obtained concerning the nature and production of growth-promoting substances in tissues *in vitro*. In contrast to this is the fact that in living organisms the existence of such growth-promoting substances is still hypothetical, although the neuro-regenerative growth substance of v. Murali¹⁸ might be of this type.

Another possible explanation of the healing-promoting effect is that it may be related to the catabolic phase of protein metabolism that follows injury (Cuthbertson⁷)—in other words, that it is a phase of the so-called adaptation reaction (Selye²⁰) associated with hyperactivity of the adenal cortex.

This relation may be conceived in many ways, the simplest being that the increase in protein breakdown products in the circulation offers a richer supply of nutrition for the proliferating fibroblasts. Cuthbertson⁷ believed that the changes which he had found to occur after injury were the result of the organism's catabolizing its reserves to meet the exigencies of repair. A combination of "wound hormone" mechanism and protein catabolism should also be considered.

It was felt that more data on the action of the healing stimulating effect would be of value in the search for an explanation of its nature and cause. The following questions seemed to be of primary interest:

- 1 The changes occurring in the healing-promoting effect with the passage of time
- 2 The difference between the healing curves of the primary and the secondary wounds
- 3 The relationship between the extent of injury and the degree of the healing stimulating effect

The wide variation in the rate of wound healing in different individuals and also in the same individuals at different times combined with the great experimental errors associated with available methods necessitated a large number of experiments to procure values that would permit estimates and comparisons. Hence in the diagrams shown each point is based on the examination of, in general, at least 40 wounds in at least ten rabbits. The corresponding tables, of which Table I is an example have been omitted and only the resulting *m*-values with the corresponding standard error have been given in the diagrams.

EFFECT OF INJURY ON WOUND HEALING

A major drawback to the method which may be mentioned is that the primary or control wound is identical with and hence inseparable from the stimulus, *i.e.* the injury. When therefore the control is altered—for example, for studying the strength of wounds at different stages in order to construct the healing curve—the stimulus is changed accordingly. Moreover, the injury is two-fold—it consists of inflicting the wound and excising it later for examination. These facts must be borne in mind when the results are evaluated.

For the experiments 800 wounds from 200 rabbits were examined.

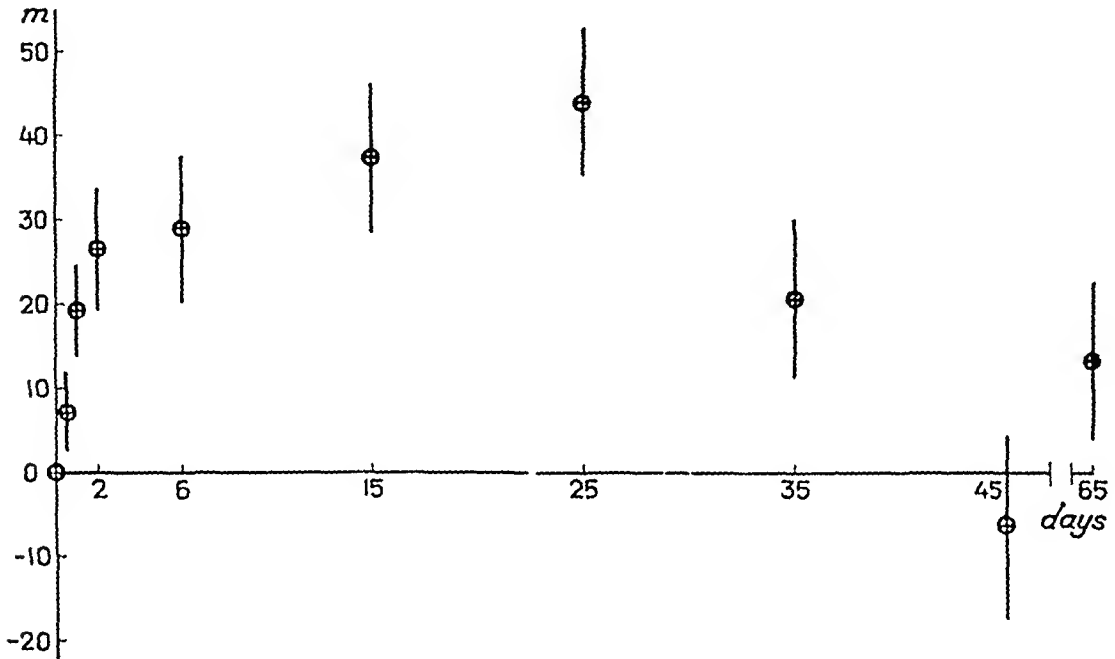


FIG. 2—The mean relative difference between the T S of the secondary and the primary wounds (= the healing-promoting effect) is represented on the vertical axis. The interval in days between the infliction of the secondary and the primary wounds is represented on the horizontal axis. The T S was measured on the 5th day throughout.

1. THE CHANGES OCCURRING IN THE HEALING-PROMOTING EFFECT WITH THE PASSAGE OF TIME

Nine groups with at least ten rabbits in each were used. The secondary wounds were made 12 and 24 hours, 2, 6, 15, 25, 35 and 65 days after the primary wounds respectively. The results are shown in the diagram (Fig. 2), each value with its standard error. The curve shows a steep rise the first two days, a flat summit up to the 25th day, and then a slow decrease towards the 45th day. The standard error increases with the time interval. This is supposedly due to the fact that uncontrolled changes in the condition of individuals occur with increasing frequency. As there was a suggestion of a negative phase at the 45th day this group was enlarged to include 16 animals but the suspicion could not be verified. If some individuals have a negative phase others might still be in the positive phase and the two would thus tend to neutralize one another. As the healing rate was expressed as the T S on the 5th day, the graph does not show the actual origin of the healing-promoting

wound effect—only that it is in action before five days and twelve hours after the first part of the injury

II THE DIFFERENCE BETWEEN THE HEALING CURVES OF THE PRIMARY AND SECONDARY WOUNDS

Eight groups were used in which the wounds were tested when they were 1, 2, 3, 4, 5, 6, 7, and 10 days of age respectively. Each group included ten rabbits except those for the second and third days, which were made larger (15 and 16 respectively), as it proved to be of interest to compare values from these two days. The interval between the primary and secondary wounds

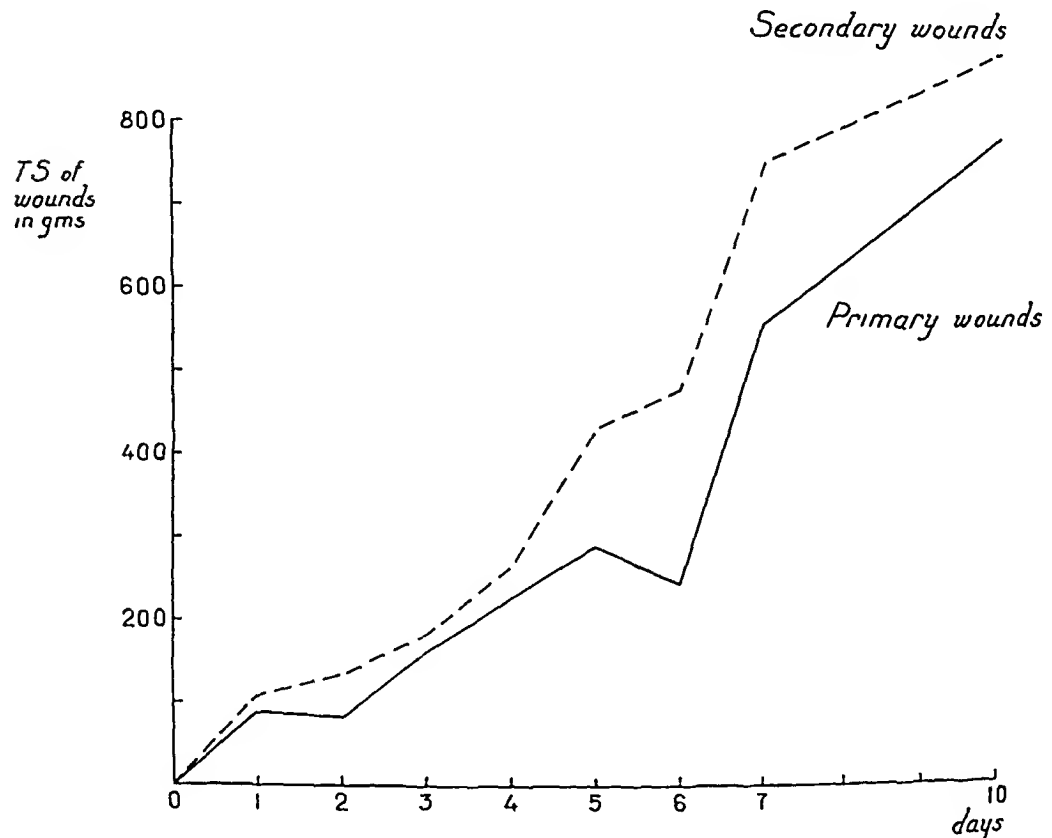


FIG 3—The mean T S in grams of the secondary and the primary wounds is represented on the vertical axis and the day on which the T S of the wound was measured, on the horizontal axis. The interval between the infliction of the primary and the secondary wounds was 15 days throughout.

was made fifteen days because the healing-promoting effect seems to be at its height at this period and rather stable (Fig 2). The healing curves for the primary and secondary wounds obtained from the means of the absolute values are shown in Figure 3 and the means of the relative differences in the T S of the primary and the secondary wounds are shown in the diagram Figure 4, in which the standard errors have also been represented.

It will be seen that the secondary wounds were stronger than the primary wounds throughout the whole period examined. As seen from Figure 4, the

EFFECT OF INJURY ON WOUND HEALING

difference is statistically significant on the 2, 5, 6, and 7 days. This diagram also shows that the relative difference reaches a maximum on the second day and again on the sixth day. The difference between the *m*-values from the second and third day is significant. In this series also the injury varied, as the wounds were excised after from one to 10 days. As the interval between the primary and the secondary wounds had been made as long as 15 days, this variation is perhaps not very disturbing, as the previous series showed the

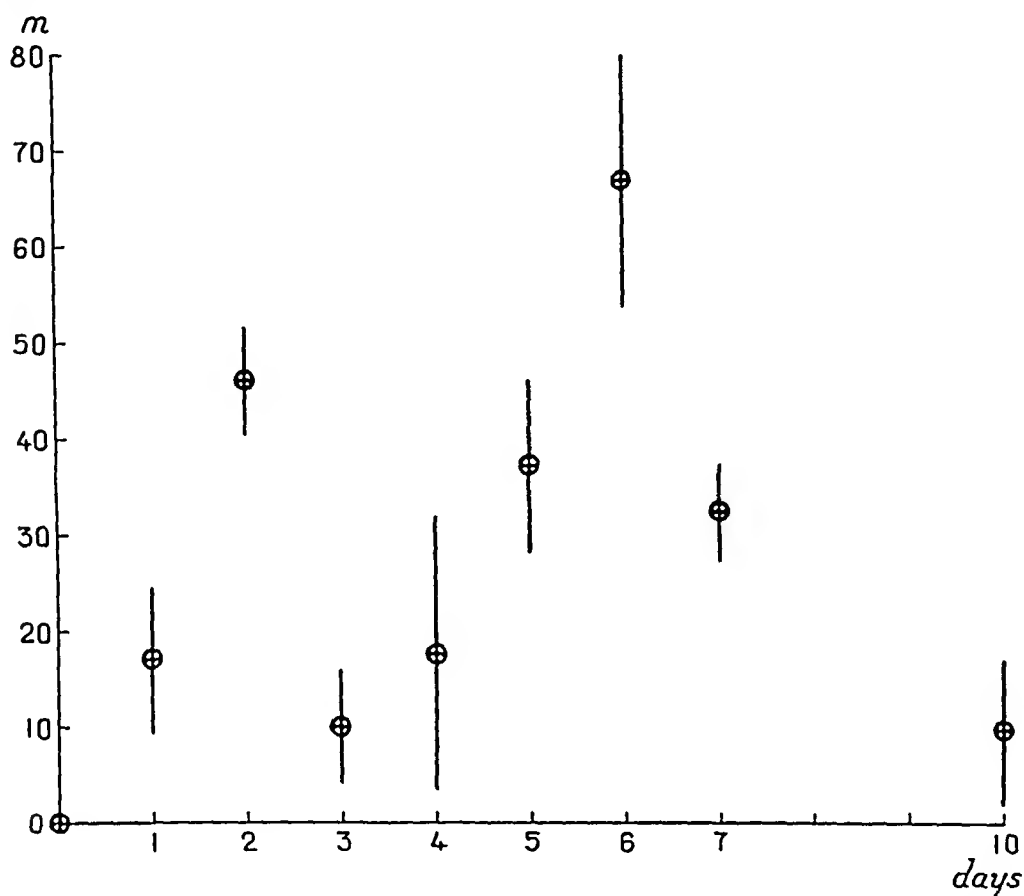


FIG 4—The mean of the relative difference in T S of the secondary and the primary wounds is represented on the vertical axis and the day on which the T S of the wound was measured, on the horizontal axis. The interval between the infliction of the primary and the secondary wounds was 15 days throughout.

healing-promoting effect to be rather stable in the period between 5 and 15 days.

III THE RELATIONSHIP BETWEEN THE EXTENT OF THE TRAUMA AND THE DEGREE OF THE HEALING-PROMOTING EFFECT

Three series were studied with 12, 11, and 10 rabbits in each respectively. The wound age was 5 days, and the interval between primary and secondary wounds was 15 days.

In the first group only one pair of wounds was made, in the second which has been used in the foregoing series as well, two pairs were made, and in the third group a long cutaneous incision was made in the abdomen when the

primary wounds were excised. The mean differences with their standard error is shown in the fifth diagram (Fig 5). It will be seen that the healing-promoting effect was greater when the injury was more extensive. The difference is not significant but may be called highly probable.

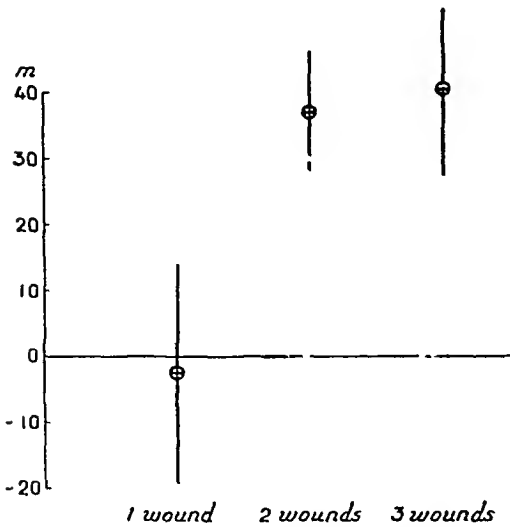


FIG 5—The mean relative difference between the secondary and the primary wounds is represented on the vertical axis and the number of wounds inflicted, on the horizontal axis. The interval between the infliction of the primary and the secondary wound was 15 days and the T S was measured on the 5th day throughout.

DISCUSSION

Ad 1 The second diagram (Fig 2) shows that the healing-promoting effect increases rapidly during the first week after the injury, reaches its full effect 3–4 weeks afterwards, and then gradually disappears towards the sixth week. The healing-promoting effect thus follows the activity of the healing process in the primary wound but continues into the period of cicatrization. It closely follows the curve for the catabolic phase of protein metabolism after injury (Cuthbertson⁸) and thus may well be related to this process. Nothing is known about specific growth promoting substances elaborated from the wound and the results speak neither for nor against this hypothesis.

Ad 2 The healing rate of the secondary wounds is more rapid than that of the primary wounds from the first day till past the tenth day of healing (Fig 3). The healing curve of a wound is the effect of at least two processes (Harvey¹⁴). There is, to start with, a lag period during the first days when the wound edges are kept together only by the wound coagulum. Then comes the period of fibroplasia when proliferating fibroblasts grow across the wound and connect the edges. The fact that the healing curve of the secondary wounds exceeds that of the primary wounds through both of the periods suggests that both of the processes mentioned are influenced by the healing-promoting effect.

When the secondary wound is stronger than the primary one as early as on the first and second day of healing it must be due to a change in the quality of the wound coagulum, as the fibroplasia hardly can have any influence at this early stage. This finding is in agreement with the experience of Bauer,² Selye²¹ and Cuthbertson⁸. Bauer² studied the coagulation of blood in connection with operations. He found the strength of the coagulum markedly elevated 24 hours after operation as compared to before. Selye²¹ and his group have had the same experience. Cuthbertson⁸ found that the fibrinogen fraction was often appreciably raised during the catabolic phase of protein metabolism.

The increase in the general healing curve beginning after the first day is due to the beginning of fibroplasia (Harvey¹⁴) When the secondary wounds are stronger than the primary during this period it is to be inferred that the healing-promoting effect stimulates fibroplasia This could be explained either as an indirect effect through the change in the quality of the wound coagulum or as a direct effect on the fibroplasia The form of the curve in Figure 4 with two separated maxima for the healing-promoting effect suggests that the fibroplasia is influenced independently of the coagulation The experiences of Alrich and Lehman¹ that anticoagulant drugs caused a decrease in the healing process as late as on the fourteenth day indicates, however, that even the later part of the healing curve may be influenced by differences in coagulation

Ad 3 The probable relationship between the extent of injury and the degree of the healing-promoting effect as illustrated by Figure 5 is in agreement with the findings of Young, Fisher and Young²⁴ that the difference between the healing rates of the primary and the secondary wounds increases as the surface area of the wound increases Bauer² found that the increase in the strength of the coagulum that occurs in connection with operations was more marked after thyroidectomies than after minor operations such as tonsillectomies (70 40)

SUMMARY

If symmetrical incisions are made successively in the skin of rabbits, the secondary wounds will heal more rapidly than the primary

Different phases of this healing-promoting effect have been studied The tensile strength (T S) of the wounds has been used as a measure of their healing rate

1 The healing-promoting effect appeared within five and a half days after injury It increased rapidly for a few days and reached its maximum between the first and the fourth week after the injury During this time the secondary wounds were 30-40% stronger than the primary ones on the fifth day of healing The healing-promoting effect disappeared 6-7 weeks after injury This course resembles the curve of the post-traumatic catabolic phase of protein metabolism

2 The healing curve of the secondary wounds exceeded that of the primary wounds through the ten first days of healing The relative difference between the T S of the primary and the secondary wounds had two maxima, one on the second day and one on the sixth day of healing This suggests that both coagulation and fibroplasia are influenced by the healing-promoting effect

3 There was probably a relationship between the extent of the injury and the degree of the healing-promoting effect

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THE SURGICAL MANAGEMENT OF CHRONIC RECURRENT INTESTINAL OBSTRUCTION DUE TO ADHESIONS*

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ONE OF THE MOST DIFFICULT PROBLEMS the internist and surgeon are called upon to manage is the patient who has been subjected to several laparotomies for the lysis of adhesions causing recurrent intestinal obstruction. As a rule after each operation the situation grows progressively worse following a transient period of improvement. Many of these patients become "intestinal cripples" and some become addicted to morphine in order to alleviate the chronic abdominal pain.

Boys¹ in 1942 critically evaluated the many methods recommended for the prophylaxis of peritoneal adhesions. He found all of the methods unsatisfactory with the exception of the intraperitoneal instillation of heparin. He pointed out, however, that although the method was effective in animal experiments, clinical experience was limited to 14 patients, one of whom died postoperatively from a massive intraperitoneal hemorrhage. We are familiar with the data on another patient in whom the outcome was fatal (22 hours postoperatively) due to a massive intraperitoneal hemorrhage.

More recently Bloor and his associates² carried out an extensive series of experiments on rabbits in an attempt to evaluate the effect of heparin in controlling the formation of adhesions and reformation of adhesions following lysis. They concluded that heparin was not effective from either viewpoint and further that many of the rabbits succumbed as a result of intraperitoneal hemorrhage and also hemorrhages into vital organs.

In view of the rather hopeless attitude of the profession towards the solution of the problem of recurrent adhesions, it is remarkable that an almost unrecognized and little known method of management has been available since 1937 when Thomas B. Noble, Jr.³ described his operation of plication of the small intestine. He subsequently reported further continued success with the method in 1939, 1942, 1943 and 1945.⁴ Although no statistics are given as to the number of cases operated upon for intestinal obstruction due to adhesions, Noble states that "no case plicated has had to be reoperated for obstruction or adhesions."

As a result of the experience obtained with the Noble operation of plication carried out on the three subjects to be reported in this paper we believe that this technic represents a significant advance in surgical therapeutics. The basic principle of this operation is that although reformation of adhesions cannot be

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prevented following their lysis, they can be *controlled*. When this is done successfully, normal motility is restored to the small intestine with consequent freedom from pain, resumption of a proper food intake, and adequate absorption of the necessary nutrients. For the technical details of the procedure the reader is referred to the papers of Noble^{3, 4}

CASE REPORTS

Case 1—Extreme malnutrition and vitamin deficiency because of adhesions. F. S., a 38-year-old white married woman consulted one of us (N. J.) in December, 1945, complaining of a sore tongue, dependent edema, weakness, vomiting, loss of weight (from a normal of 110 to 95 pounds) and abdominal pain.

The patient was well until 1921 when at the age of 14 years she was operated upon for acute appendicitis. Within one month she was reoperated upon for intestinal obstruction due to an intra-abdominal hernia. During the next year she was operated upon three times for lysis of adhesions, being carried out on each occasion for intestinal obstruction.

TABLE I

No	Date	Operation
1	June 1921	Appendectomy
2	July 1921	Exploratory laparotomy—release of an intra abdominal hernia
3	August 1921	Ventral hernioplasty—lysis of adhesions
4	November 1921	Laparotomy—lysis of adhesions
5	May 1922	Laparotomy—lysis of adhesions
6	January 1925	Laparotomy—lysis of adhesions
7	March 1932	Laparotomy—lysis of adhesions
8	April 1932	Laparotomy—lysis of adhesions and entero enterostomy
9	November 1934	Laparotomy—lysis of adhesions
10	November 1939	Laparotomy—lysis of adhesions and removal of a pelvic cyst
11	May 1940	Laparotomy—lysis of adhesions and cholecystectomy
12	June 1942	Laparotomy—lysis of adhesions and removal of right ovarian cyst and right tube

Two more operative procedures of a similar nature were necessary in 1925 and March, 1932. In April, 1932, in addition to lysis of adhesions an entero-enterostomy was performed. By 1942, 4 more operations were carried out for obstruction and adhesions, in all 11 operations. From 1932 the patient had experienced abdominal cramp-like pain the major portion of each day. By 1938 the patient had become addicted to morphine, necessitating one half of a grain (0.3 Gm) every 2 to 3 hours for control of her pain.

In spite of all these operations the patient's general condition gradually deteriorated (Table I). In October, 1943, the patient was carefully studied in the Mayo Clinic. Gastrointestinal roentgen ray series showed marked delay in emptying of the small intestine (Fig. 1, A and B). The blood calcium was 5.9 mg per cent, the serum proteins 5.4 Gm and the plasma ascorbic acid was 0.5 mg per cent. After one week of intensive nutritional therapy the patient improved and during the next year maintained a fair state of health although the abdominal pain was present daily. In September 1944, the gastrointestinal roentgen ray series taken at the Mayo Clinic again showed the same delayed emptying time but the blood calcium had risen to 9.8 mg, the serum proteins were 7.3 Gm and the plasma ascorbic acid was 1.1 mg per cent. During the next 15 months the patient had many hospital admissions for exacerbations of the intestinal obstruction but these had responded temporarily to gastric suction and parenteral fluids.

At the time of admission here, the patient appeared chronically ill, underweight and debilitated. The abdomen was distended, tympanitic, tender and scarred from 12 previous laparotomies with a ventral hernia, 12 cm in diameter covered only by skin and peritoneum.

RECURRENT INTESTINAL OBSTRUCTION

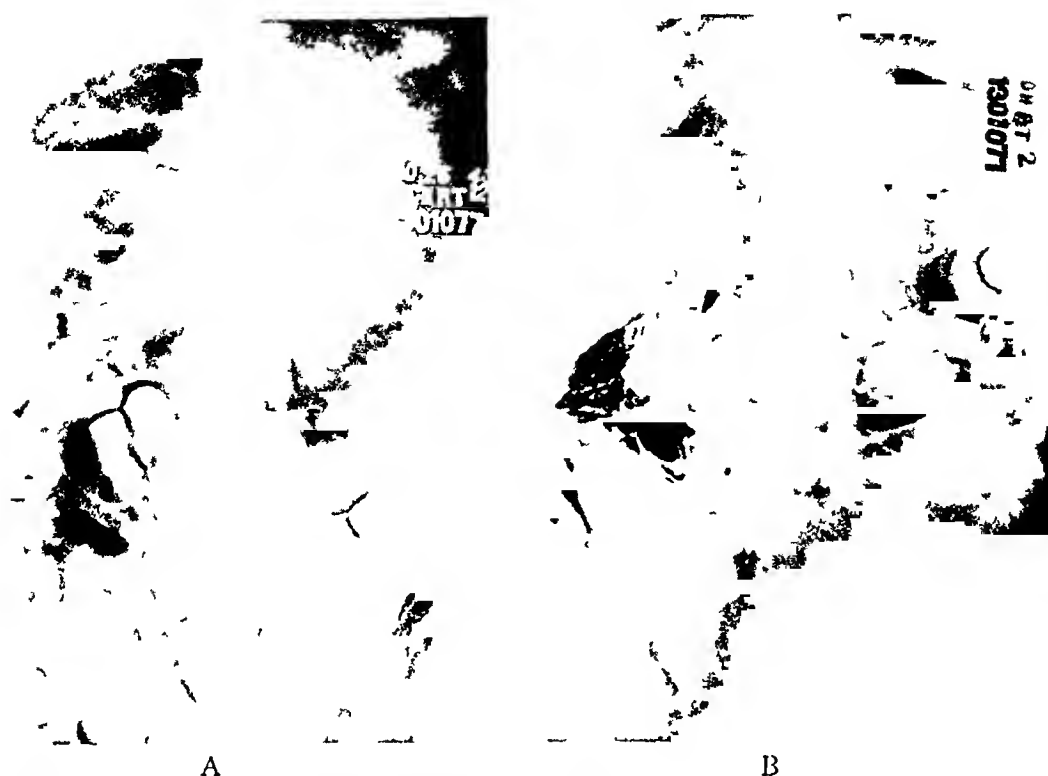


FIG 1A—A film taken 4 hours after ingestion of barium by mouth showing dilatation of loops of ileum with delay in emptying
B—Six hour film showing marked delay in emptying of small intestine



FIG 2—Flat plate of the abdomen showing marked gaseous distention — one week preoperatively
FIG 3—Barium enema demonstrating that the gaseous distention is entirely limited to the small intestine

through which distended loops of intestine cast their outline. The liver, spleen and kidneys were not palpable, ascites could not be demonstrated, no abnormal masses were felt, digital rectal and bimanual pelvic examinations were negative. Examination for signs of nutritional deficiencies showed the conjunctivae to be thin with only minimal thickening at the equators. Blood vessels of the limbic plexus penetrated a short distance into the true cornea. The angles of the mouth showed both scarring and active fissures. The tongue was thin, completely bald, and showed patches of scarlet-red color at the tip and along the lateral margins. The gums were natural. The skin was slightly dry, tanned, slightly xerotic and showed several ecchymotic areas from accidental trauma. Petechiae could not be produced by the tourniquet test. The extremities showed moderate pitting edema of the feet and ankles. The blood pressure was 120 systolic, 60 diastolic. The heart and lungs disclosed no abnormality. The neurologic examination was normal except for

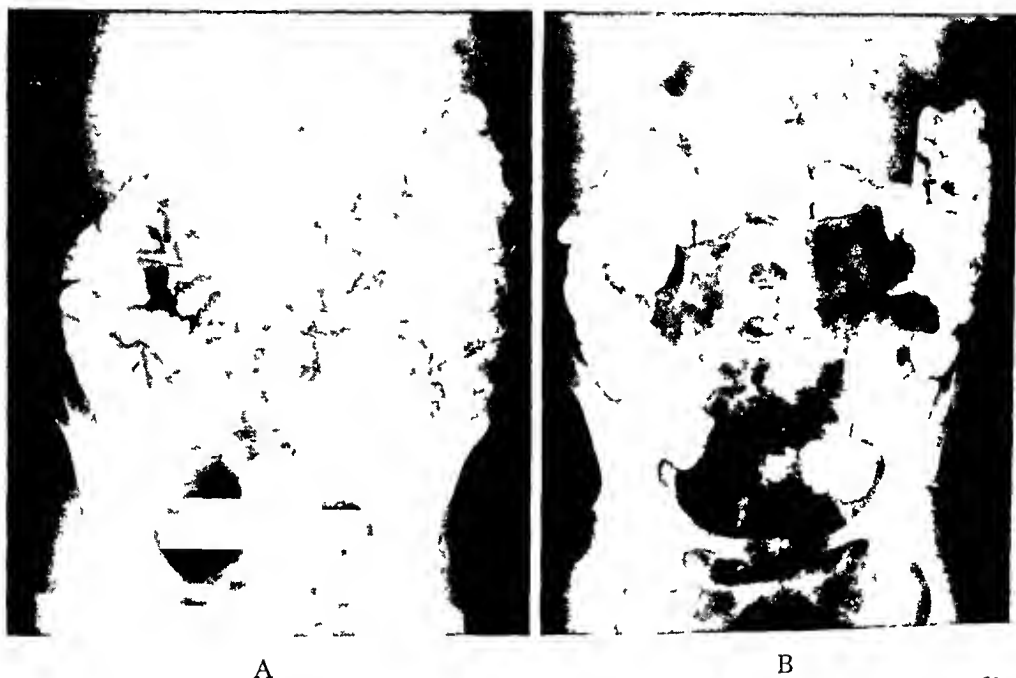


FIG 4A—Gastro-intestinal series carried out 2½ months postoperatively. A film taken 4 hours after the ingestion of barium by mouth showing most of the barium in colon.
B—Six hour film showing all of the barium out of the small intestine and in the colon.

dysesthesia of the plantar surface of the feet, and calf muscle tenderness. The red blood cell count was 3,240,000 per cubic mm, the hemoglobin was 100 Gm per 100 cc, the color index was 1.0. The white blood cell count was 9,000 per cubic mm with a normal differential count. The stained red cells showed no striking qualitative changes. The urine was negative. Blood chemical determinations per 100 cc of blood showed total proteins 5.7 Gm, albumin 3.6 Gm, globulin 2.16 Gm, ascorbic acid, 0.66 mg, vitamin A, 28 micrograms, carotene, 133 micrograms, phosphates, 5.4 units, and calcium, 100 mg.

A diagnosis was made of chronic intestinal obstruction with secondary malnutrition of calories, protein, minerals and vitamins as manifested by underweight, hypoproteinemia, edema, glossitis, vascularizing keratitis and angular stomatitis. As neither the patient nor her husband would consider surgery, medical management consisted in cajoling the patient into eating as much of a high caloric, high protein, low residue diet as possible along with supplements of protein hydrolysates and therapeutic amounts of vitamins by mouth. Folic acid therapy orally and parenterally and refined and crude liver extract parenterally failed to produce a reticulocyte response, a rise in hemoglobin or red cell

RECURRENT INTESTINAL OBSTRUCTION

changes in the tongue color or texture, or improvement in the angular stomatitis. On two occasions (February, 1946, and June, 1946) the patient was hospitalized for exacerbations of the intestinal obstruction, which responded temporarily to gastric suction and parenteral fluids. On these two occasions intravenous amino acids, blood plasma and whole citrated blood were given, which was followed by a disappearance of the abnormal red color of the tongue but without evidence of papillary regeneration. Within two weeks of discharge from the hospital, however, the redness of the tongue returned.



FIG 5—A F S, about 2 months postoperatively, weight 78 pounds
B F S, 6 months postoperatively, weight 121 pounds

On September 8, 1946, the patient was readmitted to Doctors Hospital because of an exacerbation of the chronic intestinal obstruction. Examination was essentially the same as previously described, except that she now weighed but 72 pounds and the pitting edema of the legs and sacrum was more extensive. The chemical examinations were approximately those of December, 1945, except that the vitamin A had fallen to 12 micrograms and the carotene to 16 micrograms, showing failure to absorb the large amounts of vitamin

A she had taken by mouth, and failure to either ingest or absorb carotene in her diet. Hyperperistalsis was evident and dilated loops of small bowel could be palpated readily beneath the skin at the site of the hernia. The rectum was empty. Figure 2 shows a flat plate of the abdomen and Figure 3 a barium enema which demonstrated that all of the dilated loops were of the small intestine.

Following several days of gastric suction, parenteral fluids and blood transfusions, the patient was able to take liquids by mouth. At this time the patient and her husband consented to exploratory laparotomy in hopes of being able to use the Noble plication technic. Sulfasuxidine was administered in 2 Gm doses every 4 hours for 6 days prior to the operative procedure which was carried out on September 19, 1946, by one of us (J W L Jr). It consisted in the lysis of the entire small bowel which was completely adherent to itself and to the parietal peritoneum. One area of hopelessly gnarled bowel in the region of the previous entero-enterostomy was resected and it was then necessary to carry out two end-to-end anastomoses to join, first, the distal end of the jejunum to the proximal end of a 3-foot loop which entered the gnarled mass and second, to join the distal end of this loop to the terminal ileum. Continuity having been restored, the remaining $7\frac{1}{2}$ feet of small intestine were then plicated with interrupted sutures of cotton from the ligament of Treitz to the ileo-cecal valve, each limb (or wing) of the plication being 6 to 7 inches long. The entire procedure lasted $5\frac{1}{2}$ hours and necessitated a transfusion of 2500 cc of blood.

The postoperative course was complicated by jaundice for several days during the first week and the incision and drainage of several subcutaneous abscesses from previously self-administered morphine injections. The patient progressively improved so that by the 30th postoperative day she was without edema and weighed 71 pounds. On discharge from the hospital 3 months postoperatively she weighed 100 pounds. A small bowel roentgen ray series was performed approximately $2\frac{1}{2}$ months after operation and showed a normal emptying time (Fig 4 A and B).

At the end of one postoperative month demerol was substituted for rapidly diminishing doses of morphine and after another month sterile saline was substituted for the demerol. Two weeks before discharge from the hospital the nature of the injections was explained to the patient and she adjusted well to the complete withdrawal.

During the 16 months which elapsed since discharge from the hospital the patient gained another 20 pounds, has remained free from all signs of intestinal obstruction, and all of the signs of nutritional deficiency cleared (Fig 5, A and B). Menses which had been absent or scanty for several years returned to normal by the second postoperative month and have remained regular. Normal sized loops of small bowel may be palpated easily beneath the skin at the site of the ventral hernia. There has been no resumption of any narcotic or sedative.

Case 2—Plication done in presence of acute intestinal obstruction. A 13 year-old colored girl was admitted to Presbyterian Hospital in April, 1947. Appendectomy had been performed without drainage 15 months earlier for acute appendicitis. Ten months later acute intestinal obstruction occurred, necessitating an operation for lysis of adhesions. Six weeks before this admission she was again operated upon for acute intestinal obstruction and a loop of gangrenous ileum was resected, again adhesions were divided. Cramps began 48 hours before this admission associated with continuous vomiting. Examination of the abdomen revealed tenderness and distention. A flat plate of the abdomen showed distended small intestinal loops. The Miller-Abbott tube gave poor relief and operation was carried out because the leucocyte count rose to 22,000 and the temperature to 101.2 in spite of hydration.

At operation (done by E L H) the entire ileum and jejunum were adherent. Many kinks were encountered associated with enlarged mesenteric lymph nodes. There was no evidence of gangrene but dilated vessels were present suggesting early inflammatory change. Interrupted silk sutures were used to plicate entire small intestine. Approximately

6 loops (wings) were made 12 inches in length near the ileocecal valve. All sutures were placed at the mesenteric border so that the entire lumen of the intestine was free. Post-operative convalescence was entirely uneventful. A small bowel series on the 11th postoperative day showed normal motility and emptying of the small intestine. The patient has remained well during the follow up period of 8 months. There has been no dietary restriction and she has had one to two stools a day. Some slight pain and nausea have been noted after menstrual periods.

Case 3—Case with psychotic manifestation, morphine addiction. A 30-year-old trained nurse had an appendectomy for acute appendicitis 10 years prior to admission to the Presbyterian Hospital in May, 1947. A few months following the appendectomy she was operated upon for intestinal obstruction, gangrenous bowel was resected and adhesions separated and divided. Five years later a cholecystectomy was carried out and adhesions lysed. In 1946 the patient was subjected to 3 operations at 14-day intervals for acute intestinal obstruction due to adhesions. Following the last of these procedures the patient had daily abdominal crampy pain, became addicted to morphine and was classified by the psychiatrist as an "intestinal cripple with conversion hysteria." For 2 months prior to admission the patient experienced constant crampy pain, weight loss and scanty menses.

On the 25th of May lysis of the entire small intestine was carried out followed by plication from the ligament of Treitz to the ileocecal valve by E. L. H. There were many angulations of the small intestine, the wall of which was edematous in spots and there were many enlarged mesenteric lymph nodes. During the first 24 hours postoperatively, the patient experienced severe abdominal cramps which stopped immediately on deflation of the balloon of the Miller-Abbott tube. A small bowel roentgen ray series 6 weeks postoperatively showed normal motility and emptying time. Regulation of constipation proved difficult in this case. During the 7 months follow up the patient has had no abdominal pain, has gained 15 pounds and morphine addiction has been relieved. Rehabilitation was slow, difficult but satisfactory.

COMMENT

Although the period of follow up of 18, 8 and 7 months is brief in the three cases reported above, the remarkable absence of any symptoms or signs of intestinal difficulty following the Noble plication procedure in contrast to the continuous ill health for months and years prior to plication is significant. We believe, therefore, that the results obtained with this operation deserve wider recognition and that the technic will find increasing acceptance among surgeons who are called upon to operate for intestinal obstruction due to adhesions. As Noble has stated, it places the surgeon in control of the formation of adhesions instead of allowing them to form by chance with the possibility of obstructions due to kinking and angulation. Plication of the small intestine is not technically a difficult procedure, and requires only a short time to complete after all of the adherent loops have been freed and adhesions divided, but the separation of the adhesions is a long painstaking procedure. Normal function of the small intestine is promptly restored by the operation and the ingestion and absorption of proper nutrients follow, causing the patients to gain weight and lose manifestations of their deficiencies. Two of the three patients became free of morphine addiction—one of eight years and the other of one year—and following the plication procedure both have been free from its use for 18 and seven months respectively.

CONCLUSIONS

1 The plication operation of Noble changes *uncontrolled* adhesions into *controlled* adhesions thereby preventing further attacks of intestinal obstruction due to this cause. A proper nutritional balance is restored, deficiencies clear and pain disappears. The psychotic and addiction states are relieved.

2 The histories of three cases are reviewed in detail to illustrate the great value of the procedure of plication of the small intestine.

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WEDGE OSTEOTOMY FOR FRESH INTRACAPSULAR FRACTURES OF THE NECK OF THE FEMUR*

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THAT THE PROBLEMS ASSOCIATED with intracapsular fractures of the neck of the femur are not, as yet, totally solved, is becoming more and more apparent as the end result studies from various clinics are being recorded in the literature. Many men are under the erroneous belief that by restoration of anatomic alignment and internal fixation of the fragments they will obtain good end results in 90 per cent or better of their femoral neck fractures. H B Boyd and I L George reported the following end results in a series of cases from the Campbell clinic —43.6 per cent good results, 28.1 per cent poor results and 19 per cent fair results. Of the 28.1 per cent poor results, 13.5 per cent were due to nonunion. An end result study of 102 cases of intracapsular fractures of the neck of the femur treated by the author revealed nonunion in 16 cases or 15.6 per cent. These cases were all treated by the orthodox method of reduction and internal fixation. The interesting feature of all these cases of nonunion was varying degrees of absorption of the distal fragment. Regardless of the status of the proximal fragment, whether it was viable or not, the feature of absorption in the distal fragment was always present.

It is generally believed that there are many factors responsible for nonunion such as inadequate reduction of the fragments, severe initial trauma, severed blood supply to the proximal fragment, death of the head and lack of impaction of the fragments. Nevertheless, it is true that many intracapsular fractures do unite in spite of poor anatomic alignment in the presence of a dead head and lack of impaction. It is becoming more and more obvious that there is only one real reason for nonunion and that is inadequate immobilization. If the fragments are adequately immobilized and protected for a sufficient length of time, union should occur in 100 per cent of the cases.

It is general knowledge that the abduction type of femoral neck fracture invariably goes on to bony union. Watson-Jones believes that if these fractures are adequately immobilized union will occur in 100 per cent of the cases. This is not true of the adduction type of fractures which is the most common transcervical femoral fracture. Roentgenologic study of those cases in which the femoral neck was absorbed revealed certain features which are known to all orthopedic surgeons but whose true significance I am sure has been misinterpreted or underestimated. The radiographic appearance of a segment of bone whose blood supply has been totally or partially interrupted reveals no changes in the general architecture of the bone. There is no decalcification, therefore, its density is not changed and in fact, its density may appear to be increased in

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contrast to the adjacent bone with a normal blood supply. The early phases of absorption of a femoral neck fragment reveals generalized decalcification followed later by fragmentation and absorption of the bone elements. This is indicative that destruction of the fragment is not the result of a disturbed blood supply, but due to an over active hyperemic process which causes decalcification, fragmentation and absorption of the bone fragment.



FIG 1--Note the complete absorption of the femoral neck following internal fixation with a Smith-Petersen nail. There is no radiographic evidence of a complete or partial loss of blood supply to the neck which would be demonstrated by a normal bone pattern and increased density. The bone trabeculae have disappeared, there is evidence of demineralization of the remaining bone of the base of the neck and of the upper end of the femoral shaft. These findings are consistent with a very active inflammatory process which has caused demineralization, fragmentation, and absorption of the femoral neck.

In the adduction type of fracture there is a shearing force at the fracture line at all times due to contraction of the ilio-femoral muscles. If there is any weight bearing this shearing force is increased, in the presence of inadequate immobilization a traumatic reaction is set up at the fracture site. Hence conditions are established which are responsible for absorption of the femoral neck.

There are several causative factors which are responsible for inadequate immobilization, the most common being failure to restore and maintain true anatomic alignment. In many instances the fixation pin may be poorly placed, hence, it fails to prevent torsion and shearing strains at the fracture site. Absorption around the fixation pin and at the fracture site is a common feature

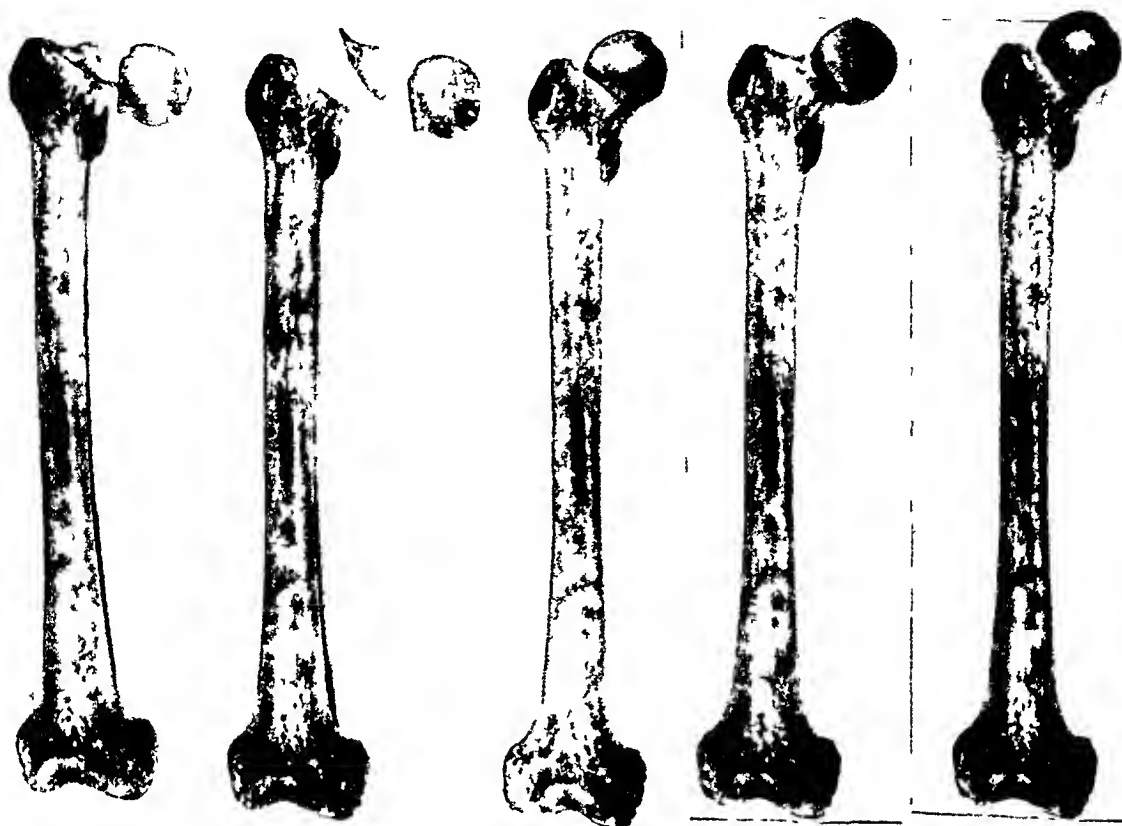


FIG 2

FIG 3

FIG 4

FIG 5

FIG 6

FIG 2—This figure portrays the usual type of adduction fracture and the relative position of the fragments upon opening the joint capsule

FIG 3—The wedge of bone has been removed from the femoral neck, note its size and shape, and the direction of the osteotomy line through the femoral neck

FIG 4—The femoral head has been placed on the femoral neck in a position of valgus on a wide base. The fragments are fixed in this position by a Smith-Petersen nail

FIG 5—Normal femur—note the position of superior margin of the articular surface of the head to the black line

FIG 6—Same femur as in Figure 5 with a wedge removed from the neck and the femoral head placed in a position of valgus. Note that the superior articular surface of the head now lies above the black line. The length of the femur is actually lengthened by increasing the angle of the femoral neck

which is followed by loss of adequate immobilization and allows the shearing forces to act freely at the fracture site

Since we have failed to obtain and maintain continuous adequate immobilization of the fragments in all cases until bony union has occurred (by restoration of anatomic alignment and internal fixation), it becomes obvious that a new and different approach to the problem must be found. This thought prompted the development of a new surgical procedure namely a wedge osteot-



FIG 7 (A) —Shows an adduction type of fracture with a "beak" shaped projection extending along the inferior aspect of the proximal fragment. This "beak" must be removed to obtain good apposition of the fragments. (B) Is the immediate postoperative roentgen ray film. (C) Note position of fragments and state of bony healing three months postoperatively. (D) Note solid bony union eight months postoperatively. Head shows no evidence of aseptic necrosis.

WEDGE OSTEOTOMY

A

B



C

D

FIG 8—(A) Shows an intracapsular fracture in which the fracture line is in a vertical plane (B) Note position of fragments after a wedge osteotomy was performed (C) Note evidence of bony healing six weeks postoperatively (D) Complete healing is evident eight months postoperatively, because the nail had pierced the head on insertion it was removed

omy through the femoral neck done in fresh adduction fractures. Essentially it consists in the conversion of an adduction fracture to an *abduction* fracture by removing a wedge of bone from the femoral neck. All shearing forces at the fracture site, regardless of their origin, are now converted into impacting forces which enhance healing. This preliminary report of 22 cases is being submitted with the hope that the procedure will be adopted by more surgeons interested in femoral neck fractures. At a later date the end result studies of a larger series of cases will be presented.

TECHNIC OF OPERATION

The hip joint is exposed through a Smith-Petersen incision which is extended backward to the posterior portion of the tensor fascia femoris muscle. The tensor fascia femoris muscle is divided transversely about $3\frac{1}{2}$ inches to 4 inches below the tip of the greater trochanter. The fracture site is exposed by a vertical incision in the joint capsule. If more exposure is needed, it may be necessary to make transverse incisions in the capsule above and below the vertical incision. By external rotation of the extremity the fracture site is readily brought into view. At this point a very common and important finding should be mentioned. In eight of the cases operated upon to date the proximal fragment, whether it was short or long, possessed an extension of the femoral neck along its inferior aspect. This projection was "beak" shaped and prevented reposition of the proximal fragment into a valgus position; therefore, it had to be removed in every instance. It is obvious that this "beak" would offer great resistance to any closed maneuver which attempted to place the proximal fragment in a position of valgus. This proved to be true at operation; it was impossible to attain the valgus position and still have good approximation of the fractured surfaces unless the "beak" was removed.

The next step is the removal of a wedge of bone from the distal fragment of the neck with its base superiorly and its apex inferiorly. The width of the base depends upon the obliquity of the fracture line. The more the fracture line approaches the vertical the greater the width of the base. The wedge should be of sufficient size so that an adequate support is created for the proximal fragment. The "beak," if present, is then removed with an osteotome from the proximal fragment.

The shaft is next internally rotated and the proximal fragment levered into its new position of valgus. The fragments are locked by internal rotation and abduction of the femoral shaft.

Under direct vision the fragments are locked together with a Smith-Petersen nail. The capsule is closed with interrupted sutures and the incision is closed in the usual fashion.

POSTOPERATIVE MANAGEMENT

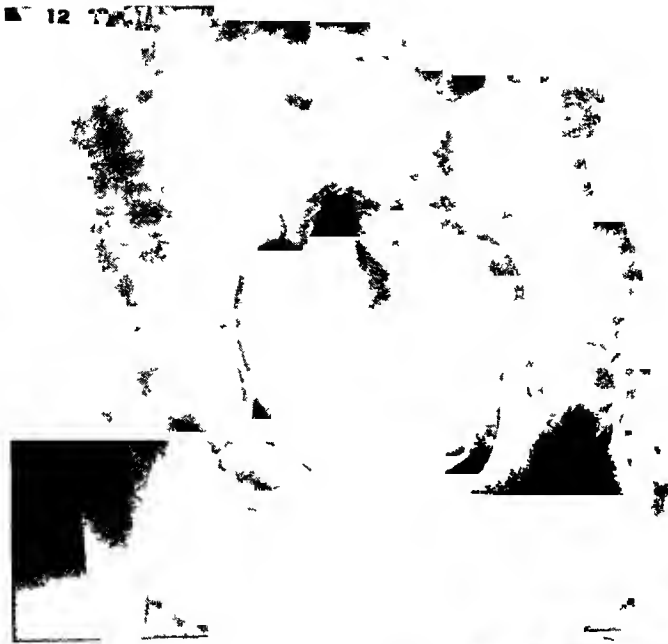
These patients are allowed to sit at the edge of the bed on the first or second postoperative day. On the third day they are allowed out of bed in a chair and on the fourth day they are made to stand on crutches, partial weight

WEDGE OSTEOTOMY



FIG 9—(A) Shows typical adduction type of fracture with a "beak" along the inferior aspect of the proximal fragment (B) Immediate postoperative film (C) Note status of bony union four months postoperatively

A



B



C

FIG 10—(A) Adduction type of fracture with considerable upward displacement of the shaft (B) Note valgus position of head in immediate postoperative film (C) Note status of bony union four months postoperatively

bearing is allowed on the fractured extremity. The patients are ambulatory, on crutches, by the end of ten days. A check-up radiographic examination is made every six weeks and at the end of four and one-half to five months they are made to discard their crutches.

To date no evidence of avascular necrosis of the head has appeared in any of the cases, this, however, may occur at a later date.

ANALYSIS OF CASES

Twenty-two cases with an adduction type of transcervical fracture of the neck of the femur are presented. The youngest patient was 62 years old, the oldest patient was 83 years old. In eight cases the proximal fragment had a "beak" like projection along its inferior surface. A wedge osteotomy was done in each case as described above and the proximal fragment was placed in a position of valgus. The fragments were fixed by a Smith-Petersen nail. Union was obtained in all cases and definite bony union was evident in the check-up radiographic examination 12 to 16 weeks after operation. No absorption of the femoral neck occurred in any of the cases. There was no evidence of loss of position of the proximal fragment or of absorption around the fixation pins. To date no evidence of an aseptic necrosis of the femoral heads has been noted although sufficient time has not yet elapsed to pass final judgment. The first case in this series is 12 months old, the last case is 4½ months old. There were no deaths.

DISCUSSION

In view of the results to date, this is a justifiable procedure. In the hands of men competent in hip surgery this is not a formidable operation. Many orthopedic surgeons today have gone back to the open method of internal fixation of femoral neck fractures, their morbidity and end results do not differ from the end results of those using the closed methods. This procedure adds one more step to the open procedure, namely the removal of a wedge of bone from the distal fragment. The only real difficulty in the procedure may be the presence of the "beak" of bone on the proximal fragment, this difficulty is overcome by removal of the projecting spicule of bone.

The length of the limb is not sacrificed as a result of this procedure. In fact, the length of the extremity is in most instances increased as much as one eighth to one fourth of an inch. This is due to the extreme valgus position of the proximal fragment. Figures 5 and 6 illustrate this point.

What the fate of the femoral heads is going to be is still undecided. Undoubtedly a certain number will develop aseptic necrosis because of an interrupted blood supply at the time of the initial trauma. In this small series the features of aseptic necrosis as yet have not manifested themselves.

Recent Follow-up Study on Reported Cases

Since this article was submitted for publication, another follow-up study has been made of the reported cases. The oldest case is now 20 months and the

most recent is one year following operation. The survey revealed that all the reported cases united by bony union, however, we have had two instances of aseptic necrosis of the femoral head.

Sixteen other cases have been operated upon. In this second group there were found three cases of absorption of the femoral neck. Two of these cases can be attributed to the fact that the patients insisted upon walking. In the third case failure was due to faulty operative technic. At the time of the operation, considerable difficulty was encountered in aligning the femoral head in a position of abduction. More extensive surgery than is usually required was necessary in order to get proper alignment. One is forced to believe, therefore, that this added trauma and the manipulation was directly responsible for the absorption of the femoral neck.

It might be interesting to note that in two other instances the three-flanged nail would not penetrate the femoral head. In both cases it was necessary to remove the femoral head and do a primary arthroplasty of the hip. After operation the heads were placed upon a wooden block and an attempt was made to drive the nail through. In one instance, the end of the three-flanged nail splintered but did not penetrate the head. In the other instance, the head disintegrated into several fragments but did not allow penetration of the nail. These two cases are recorded because they provide another explanation of why some blind nailings fail. It may be possible that in a small percentage of cases the increased density of the head prohibits any type of internal fixation. A more detailed report will be made on the entire series at a later date.

TISSUE-CULTURE EVALUATION OF THE VIABILITY OF BLOOD VESSELS STORED BY REFRIGERATION*

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FOR SEVERAL DECADES experimental surgeons have been studying methods for the storage of vascular segments and have been working toward the goal of using such stored vessels as grafts whenever it is necessary to bridge a large gap in the arterial or venous system. Vascular segments have been stored in vaseline, moist air, saline, Ringer's solution, and other media, at temperatures slightly above freezing^{6, 7, 8}. Vessels have also been stored in a frozen state^{2, 3, 10}. To evaluate the viability of a stored vessel, examinations have generally been made by studying its histological detail or by implanting a portion of it as a graft and observing it during a survival period in a living animal. The viability of stored tissues destined for grafts has been tested by tissue-culture methods on only a few occasions,^{8, 23} but such tests have not been applied to the study of blood vessels. It is the purpose of the present communication to record our observations on tissue-culture studies which were made on arterial segments (animal and human) which were stored by various methods**

METHODS EMPLOYED FOR VESSEL STORAGE

First Method—Storage in 10 Per Cent Homologous Serum and Balanced Salt Solution

Portions of aorta or its large branches were obtained under aseptic conditions within five hours after death from mongrel dogs of various ages, young adult human beings, a young baboon, and a young pig. Following ligation of branches with 0000 silk the vessels were divided into segments 2 to 6 cm long which were suitable for grafting and into control segments 0.3 to 1 cm long. The vessel sections were held temporarily in sterile "Ringer's"[†] or balanced

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** This study has been greatly facilitated by the generous assistance of Dr. John F. Enders, The Children's Hospital, Boston, Mass., and Dr. John H. Hanks, Department of Bacteriology, Harvard Medical School, Boston, Mass., who suggested the methods of storage and of tissue culture and guided the project at many stages.

† The "Ringer's" solution had the following composition per liter: NaCl 7 Gm, Na Lactate 2.7 Gm, KCl 0.4 Gm, CaCl₂ 0.2 Gm.

salt solution (hereafter called "BSS"),* and as soon as possible thereafter (generally within 30 minutes and always within 2 hours) were placed individually in sterile 25 or 50 cc Erhlenmeyer flasks containing 10 or 20 cc of the following nutrient medium BSS 85 per cent, homologous serum** 10 per cent, penicillin and streptomycin (1000 units each per cc) 5 per cent. During most of this study, flasks were stoppered with cotton and the volume of fluid was so chosen that it just covered the tissue (Fig 1). Segments for tissue-



FIG 1—Blood vessel stored in flask containing 10% homologous serum and balanced salt solution

culture or histological control were generally included in the flasks, with the graft segments but occasionally in the earlier part of the work they were placed in separate flasks. Recently it has seemed better practice to close the flasks with a tightly-fitting skirt type rubber stopper. Most of the flasks were stored at 1° to 4° C in the hospital blood bank refrigerator, a smaller number were held in a common domestic refrigerator, the temperature of which varied between 6° and 11° C. In some instances the nutrient medium was renewed at intervals, generally every two weeks. During storage the flasks were carefully observed for cloudiness, growth of fungi, or changes in pH. In a few instances bacteriological studies were made. These included culture of the centrifuged and washed sediment from the storage media and measurement of

* BSS solution was supplied by Dr J H Hanks. It resembles "Tyrode's" solution and was prepared as follows:

Stock solution, contents per 250 cc: NaCl 20 Gm, KCl 1 Gm, $MgSO_4 \cdot 7H_2O$ 0.2 Gm, $MgCl_2 \cdot 6H_2O$ 0.2 Gm, $CaCl_2$ 0.35 Gm (dissolved separately), Na_2HPO_4 0.15 Gm (0.38 Gm of $Na_2HPO_4 \cdot 12H_2O$), KH_2PO_4 0.15 Gm, glucose 2.5 Gm, 0.4% phenol red 12.5 cc.

Buffer 1.4% $NaHCO_3$

The stock solution was stored at room temperature with 1 cc chloroform. The final solution was made by diluting the stock 1:10, autoclaving, and adding 0.5 cc (previously autoclaved) buffer per 20 cc. This was stored in cotton-stoppered containers in the ice box, which caused pH equilibration at about pH 7.6.

A somewhat similar solution prepared according to Simms' formula is available commercially from Microbiological Associates, Flemington, New Jersey.

** Baboon and pig vessels were stored in dog serum. Fresh or frozen serum was employed.

the antibacterial titer of the storage fluid from time to time *

Second Method—Storage in Helium under Pressure

Segments of dog vessels were washed in BSS, placed in test tubes, and then stoppered tightly. The air was replaced with medicinal-grade helium at 76 cm Hg above atmospheric pressure and the tubes were stored at 0° C.

Third Method—Storage in Salt Solutions

Several experiments were carried out, placing sections of dog arteries in cotton-stoppered 50 cc flasks in normal saline, "Ringer's" solution, or BSS. In each instance penicillin and streptomycin solution was added (giving a final concentration of each drug of 50 units per cc). These were stored at 6° to 11° C.

Fourth Method—Storage in 100 Per Cent Serum

Dog vessel segments were placed in 10 cc of autologous serum in 25 cc cotton-stoppered flasks. Their refrigeration temperature was 1° to 4° C. No antibiotics were added.

Fifth Method—Storage in Serum Ultrafiltrate, With and Without 10 Per Cent Homologous Serum

Dog vessel segments were placed in 50 cc flasks containing 20 cc of fluid which was composed of serum ultrafiltrates** 33 per cent and BSS 67 per cent. To each flask was added penicillin-streptomycin (final concentration 50 units per cc), and to about half, 2 cc homologous serum. Approximately half of the tubes were closed with sterile cotton and the remainder with skirt type rubber stoppers. Some of the flasks were stored at 1° to 4° C and some at 6° to 11° C.

Sixth Method—Storage of Vessels in Frozen State

Segments of dog vessels of varying size were placed individually in sealed 15 mm Pyrex test tubes or sealed one-half inch heavy copper tubes and frozen in a variety of ways to approximately -70° C. They were all then stored at about -76° C in a solid carbon dioxide deep-freeze †. When specimens were to be used for grafting or for tissue-culture studies, they were thawed by immersing the tubes for 3 to 10 minutes in a 37° C water bath.

* The bacteriologic examinations were kindly performed by George E. Foley, Department of Pathology of The Children's Hospital.

** Serum ultrafiltrate is obtainable commercially from Microbiological Associates, Flemington, New Jersey.

† Most of these experiments were carried out in conjunction with Dr. C. A. Hufnagel, Department of Surgery, Peter Bent Brigham Hospital, Boston, who shared the vessels stored for grafting.

The methods of freezing were as follows

A Glass tubes containing air at atmospheric pressure were immersed in a mixture of alcohol and solid carbon dioxide⁴

B Sealed glass tubes were filled with helium at 20 to 152 cm Hg above atmospheric pressure and frozen by immersion in an alcohol-carbon dioxide mixture¹⁶

C Glass tubes with helium at 76 cm Hg above atmospheric pressure were slowly brought to -70° C in about 30 minutes rather than rapidly as in A and B

D Copper tubes flushed with sterile mineral oil and filled with helium at about 152 cm Hg above atmospheric pressure were immersed in an

FIG 2

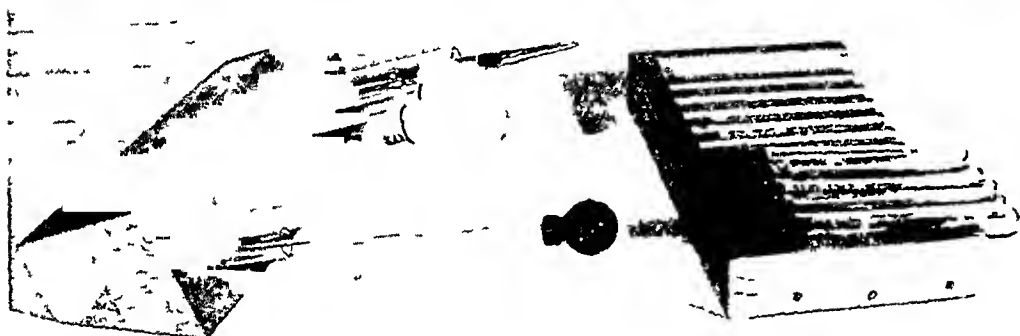


FIG 3

FIG 2—Right angle pipette for transferring tissue to culture tube. Made by drawing out 8 mm soft, glass tubing

FIG 3—Left—Wood block used for holding reagents and Bard-Parker knives. Right—Test tube holder employed for setting up cultures and for slanting them in the incubator (after Hanks)

ether-carbon dioxide mixture for very rapid freezing. To ascertain if the copper *per se* was toxic to the tissue, several tubes were not frozen but were stored at 6° to 11° C instead.

METHODS EMPLOYED FOR TISSUE-CULTURE STUDIES

When a portion of vessel was to be cultured, it was placed in a sterile Petri dish, washed with BSS, and cut into 1 to 2 mm squares the full thickness of the vessel wall with two No. 11 Bard-Parker knives which had been steril-

ized by storage in 95 per cent ethyl alcohol and ignition of the alcohol. The BSS was then pipetted off and the following transfer medium substituted: Homologous serum* 2 cc, BSS 2.5 cc, beef embryo juice 0.5 cc, penicillin and streptomycin solution (1000 units each per cc) 0.5 cc. Sterile acid-cleaned 125 x 15 mm test tubes were prepared by rinsing their entire lower half with one drop of chicken plasma†. Four pieces of a given tissue were then transferred to each of two tubes with a small right angle pipette (Fig. 2). After aligning these fragments in the lower one-half of the tube, 4 to 6 drops of the transfer medium were added and the tubes rotated and tilted to mix the medium and the chicken plasma thoroughly (Fig. 4). The tubes were then placed flat, with the tissue down. When firm clotting had occurred (usually after 5 to 10 minutes) 10 to 15 additional drops of medium were added with care to wet the entire surface of the clot. The tubes were then closed tightly with rubber stoppers, slightly slanted (Fig. 3), and placed in a 37° C incubator. Readings were taken at intervals for one, and occasionally two weeks, by examining the edges of the tissue explants for cell growth under low power and by observing changes in pH. Any increase in acidity due to tissue metabolism was shown by change of color from pink (pH 7.4-7.6) to orange (pH 7.2-6.8) to yellow (below pH 6.8). The fluid in the tubes was not renewed but one drop of bicarbonate buffer was added if the fluid became yellow. When growth occurred, a rough index of its extent was obtained by recording the proportion of explant circumference supporting cells. Growth consisted of fibroblastic proliferation. Since endothelium is difficult or impossible to differentiate from this²¹ and may actually transform into fibroblasts²⁷ no special effort was made to distinguish it.

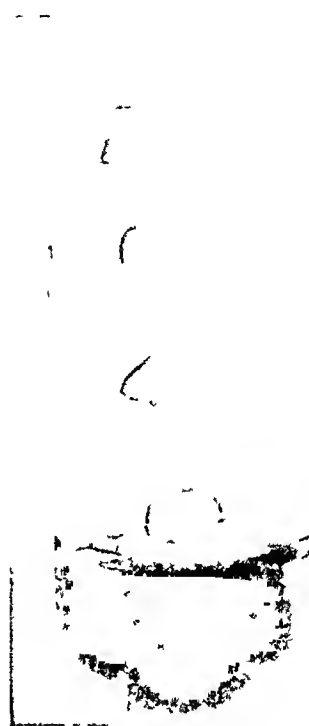


FIG. 4 — Tissue cultures showing tissue fragments in proper position and correct supernatant.

* Dog serum was used for the baboon and the pig vessels. The serum was centrifuged twice and stored in 2 cc amounts at -20° to -25° C.

** Supplied by Dr. J. H. Hanks. Three to 5-inch beef embryos and an equivalent volume of BSS solution were mixed in a Waring blender for 15 minutes. The suspension was centrifuged for 30 minutes at high speed and the supernatant fluid collected and respun. The resultant fluid was tested for sterility and stored in small amounts at -20° to -25° C. Before use, the unfrozen material was re-centrifuged.

† Supplied by Dr. J. H. Hanks. Chicken blood was taken in a 10 cc syringe containing 0.2 cc of 10% sodium citrate, centrifuged twice, and stored in 1 to 2 cc amounts in cotton-stoppered tubes at -20° to -25° C.

Some tissue cultures were photographed fresh, while others were fixed in Zenker's solution, cut at 3 to 5 mu, and stained with hematoxylin and eosine

OBSERVATIONS ON VESSELS STORED BY THE VARIOUS METHODS

I Tissue Preserved in 10 Per Cent Serum in BSS

Vessels stored within six hours following death (of animal or human) showed no consistent diminution in vitality due to this delay. Most of the tissue taken near six hours, however, grew less luxuriously than tissue taken within two to three hours. Variations in body size (of animal or human), the temperature of the room or icebox in which a body had been kept before the blood vessels were removed obviously presented factors which had a direct bearing on the viability of the removed tissues. The probability that vessel viability falls off rather sharply after death is supported by one human example, in this instance the vessels were obtained between $6\frac{1}{2}$ and $7\frac{1}{2}$ hours after death and showed no growth on tissue culture. Except for this, data are not available beyond the six-hour period.

Bacterial contamination is manifested by the appearance of cloudiness in the storage medium or by an abrupt change in its pH. It is also made evident by similar changes plus the growth of colonies in the tissue-culture tubes. Bacterial growth was not observed in stored dog tissue and although routine cultures were not taken, the culture of spun sediment from several suspicious flasks on various occasions yielded no growth. Human tissue stored before six hours was without demonstrable bacterial contamination. When slight cloudiness appeared after several weeks of storage, the spun sediment generally consisted of amorphous debris. In the one case where human vessels were obtained after six hours, cloudiness and demonstrable bacterial contamination became evident in each of eight flasks starting at 15 days. The contaminant (probably present when the tissue was first preserved) was *Ps aeruginosa*. Once it had made its appearance, it could not be suppressed with eight times the original antibiotic concentration.

In contradistinction to bacterial contamination, growth of fungi occurred sufficiently frequently (under 5 per cent) in stored dog tissue to constitute a nuisance, but was not observed in stored human tissue. Such contamination was generally not evident until three or four weeks of storage. Its appearance was unrelated to the type of stopper used. It was easily recognized by inspection of the flasks, all of which were immediately discarded.

The results of antibiotic titer tests were surprising and gratifying (Table I). Although the very high effective antibacterial activity cannot readily be explained, it probably results from the combined action of the specific agents, the serum, and possibly even the stored tissue. This high antibacterial titer, together with the low storage temperature, probably explains the very low incidence of bacterial contamination which was encountered.

Dog aorta maintained in cotton-stoppered flasks at 1° to 4° C showed growth comparable to that of the fresh controls for approximately 20 days. After this time both the per cent of tissue pieces exhibiting growth and the

extent of growth apparently fell slowly, but substantial growth was demonstrated after storage periods of 50 days (Figs 5 and 7) Tissue cultured during the first three weeks of storage frequently showed earlier and more luxuriant growth than the controls, suggesting a diminution of the usual adult growth inhibition^{28, 29} Tissues stored for more than three weeks generally exhibited a lag in the appearance of growth For all storage intervals, the extent of growth paralleled the percentage of viable tissues

Dog aorta stored at 6° to 11° C in cotton-stoppered flasks grew more luxuriantly than that stored at 1° to 4° C for two weeks but did no better at four weeks

TABLE I—Antibacterial Titer of 10% Serum and BSS Storage Medium and Its Components

Material Studied	Length of Use	Oxford Units/cc Equivalent Penicillin Titer*	Mcg /cc Equivalent Streptomycin Titer**
Dog serum	Fresh-frozen	0	640
Human serum	Fresh-frozen	0	640
BSS	Fresh	0	0
BSS plus dog serum	Fresh	0	640
BSS dog serum, penicillin and streptomycin	Fresh	1280	2000
(standard storage medium)	Fresh	512	6400
BSS dog serum penicillin and streptomycin blood vessel	14 days	640	1000
BSS human serum penicillin and streptomycin blood vessel	23 days	640	2000
	25 days	512	6400
	26 days	512	5120

* Assay organism *B subtilis* strain SD¹⁶

** Assay organism *B circulans*¹⁵

The antibiotic assays were done according to the standard methods of the Food and Drug Administration

A smaller series of cultures of human vessels stored at 1° to 4° C showed roughly comparable results (Table II, Fig 6)

Pig and baboon aortas stored in 10 per cent dog serum and BSS maintained viability for about two weeks

Renewing the nutrient medium in the storage flasks at two week intervals produced no definite growth improvement, and since it was shown that the original antibiotic titer was well maintained, the practice was discontinued

In all of the cotton-stoppered series the storage of small (less than 1 cm) portions of tissue alone adversely affected their chance of survival Larger pieces of tissue produced an appreciable drop in pH of the storage medium within a few days to a week, the flasks containing only small tissue fragments at best maintained a constant pH but generally became more alkaline with time Small fragments which had been stored alone regularly failed to show growth after short intervals In order to give an overall picture, results obtained when small pieces of tissue were stored alone have not been excluded

FIG 5

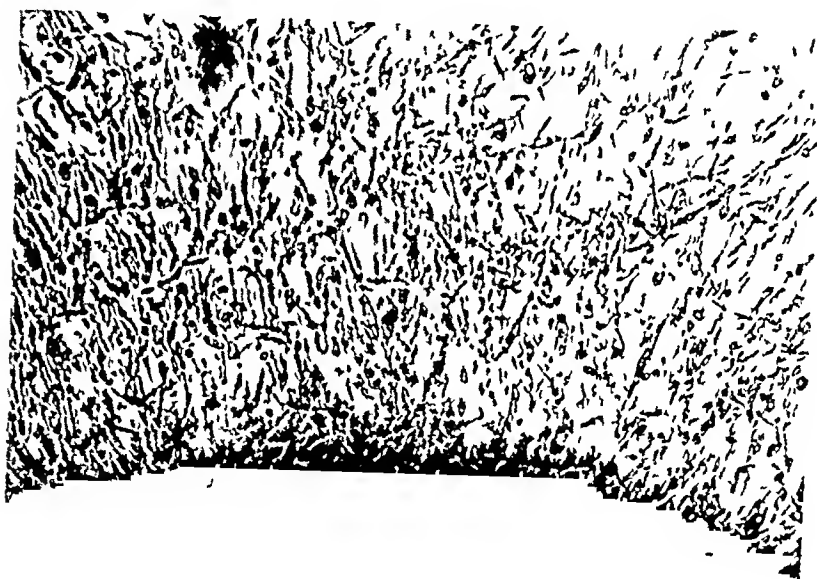


FIG 6

FIG 5—Photomicrograph unstained $\times 55$, of dog aorta tissue-culture. The aorta had been stored for 50 days in 10% homologous serum and BSS at 1° to 4° C and had then been cultured for 7 days. There is active growth of fibroblasts.

FIG 6—Photomicrograph, unstained $\times 55$, of human aorta tissue-culture. The aorta had been stored 28 days in 10% homologous serum and BSS at 1° to 4° C and had then been cultured for 7 days. There is active growth of fibroblasts.

TABLE II

Results of tissue-cultures of human aorta stored in 10% serum and BSS at 1° to 4° C Three fresh controls showed 80% growth Each percentage represents studies on 8 pieces of tissue		
Duration of Storage	Percentage of Pieces Growing	
	Cotton- Stoppered Flask	Rubber- Stoppered Flask
1 day	75	
2 days	37 5	
3 days	62 5	100
7 days	87 5, 0, 0	
14 days	87 5, 12 5, 0, 0	100
16 days	37 5	100
21 days	75, 0 0	
26 days		87 5
27 days	62 5 0	87 5
36 days	25	
37 days		75
42 days	0	
49 days	0	

Tissue-culture Studies on Dog Blood Vessels

Vessels Stored in 10% Hamologaus Serum and BSS at 1° to 4° C,
 (in cotton-stoppered flasks)

Each verticol line represents a single experiment of 8 places of
 tissue read after 7 days tissue culture at 37° C

12 Fresh control experiments overaged 94.8% growth
 0 = No growth

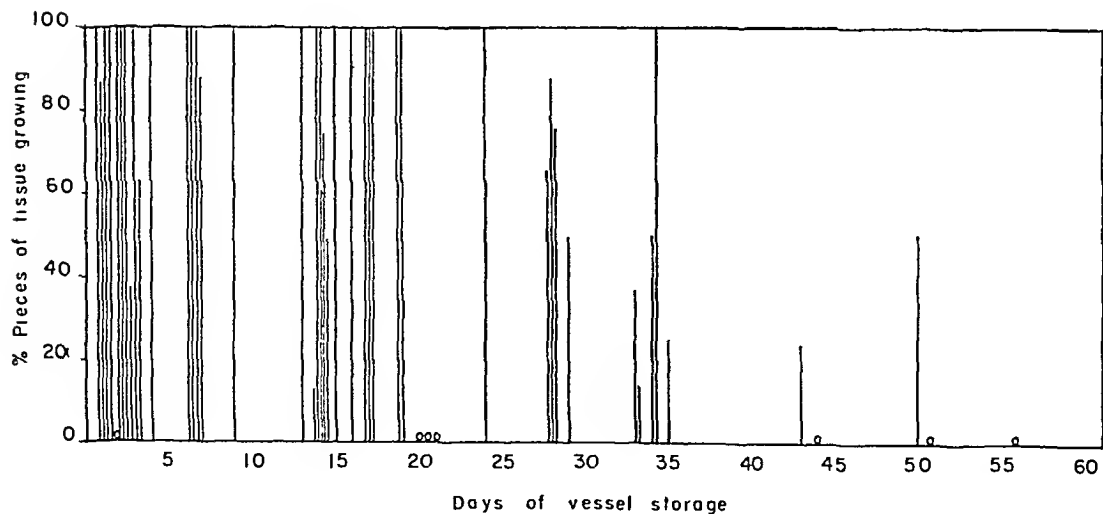


FIG 7—Results of culture of specimens of dog aorta which had been stored for vary-
 ing periods of time. The vessels could be grown in a high percentage of cases after 35
 days of preservation, and in one instance could be grown after 50 days of storage

from Fig 7 and Table II. A breakdown of some of the human data, however, shows how important this factor of small size is in influencing viability (Table III). For this reason, whenever it has been necessary to store small tissue pieces in cotton-stoppered flasks, the viability of the small piece can be enhanced by including a large piece of tissue in the flask.

TABLE III—*Effect of Tissue Size on Survival Blood Vessels, Human, Stored in 10% Serum and BSS at 1° to 4° C as Large and Small Pieces and Then Cultured at 37° C for 7 days*

Length of Vessel Storage	Stored as Large pieces (3-4 cm)		Stored as Small pieces (less than 1 cm)	
	Number Pieces Cultured	Percentage Growth	Number Pieces Cultured	Percentage Growth
1 day			8	75
3 days			8	62.5
7 days			24	16
14 days	8	87.5	16	6.3
21 days	8	75	16	0
28 days	8	62.5	8	0

TABLE IV—*A Comparison of the Effects of Storage Temperatures and the Method of Sealing of Storage Flasks on Growth of Dog Arteries Preserved in 10% Serum and BSS. The Various Groups of Tissue-Cultures Were Carried Out Concurrently*

Duration of Storage	Storage Temperature	Percentage of Pieces Growing	
		Cotton stoppered	Rubber stoppered
14 days (M)	1°-4° C	100	100
17 days (L)		100	100
17 days (M)		100	100
17 days (S)		100	100
28 days (M)		62.5	100
33 days (L)		37.5	100
33 days (S)		12.5	100
44 days (M)		0	50
57 days (M)	6°-11° C		0
17 days (M)		100	100
33 days (M)		Contaminated	100

Four fresh controls showed 100% growth

Each percentage represents studies on 8 pieces of tissue

L—approximately 6 cm vessel segment

M—2 to 3 cm vessel segment

S—1 cm or smaller vessel segment

In contrast to the results observed on tissues stored in cotton-stoppered flasks, blood vessels stored in rubber-stoppered flasks either at 1° to 4° C or at 6° to 11° C showed more reliable growth (Tables II and IV). When stored in rubber-covered flasks, the size of the tissue had very little effect on viability and in one instance 1 cm sections of dog carotid artery grew as well after 33 days' storage as at 17 days. A cotton-stoppered control grew well at 17 days but very poorly at 33 days. The data on vessels stored at 6° to 11° C is limited but indicates that this storage temperature is satisfactory.

Vessels in sealed flasks produced an appreciable drop in pH much more quickly than did similar vessels in cotton-stoppered flasks. Generally, the original pink color (pH 7.6) gave way to an orange (pH 7.2–6.8) within 12 to 24 hours. When this drop failed to occur, tissue-culture produced no growth. This early pH drop is therefore suggested as an important gross indication of viability. Once the pH had fallen to 6.8–7.2, it changed very slowly thereafter.

Blood vessels stored in 10 per cent serum and BSS were slightly yellowish in color, but showed no important edema. They retained their normal con-



FIG 8—Section of stored dog aorta, showing excellent preservation of architectural detail. Hematoxylin and eosine. Vessel had been stored in 10% homologous serum and BSS at 1° to 4° C for 56 days.

sistency and were indistinguishable from fresh vessels in suturing properties. Histological sections of tissue stored as long as 56 days showed preservation of architecture and cell detail (Fig 8). Aortic grafts of stored tissue were generally successful, dehiscence and thrombosis rarely occurred (Fig 9).

II Tissue Preserved in Helium under Pressure at 0° C

Tissue preserved by this method showed rapidly diminishing viability with no growth after one week and the segments were strongly acid in reaction indicating an excess accumulation of metabolites.

III Vessels Preserved in Salt Solutions

Dog aortas held in BSS, normal saline, or "Ringer's" solution at 6° to 11° C for periods up to four days grew almost as well as fresh controls.

After this time, there was a constant loss of viability and by 14 days' storage only a small proportion of the explanted tissue pieces grew. For this particular set of experiments, the normal saline was the most favorable and the "Ringer's" solution the least favorable storage medium.



FIG 9—Graft of abdominal aorta (dog to dog). The grafted section had been stored in 10% homologous serum and balanced salt solution for 6 days and then had been implanted into a recipient animal which was kept for 6 months before sacrifice.

IV Vessels Preserved in 100 Per Cent Serum

Tissue stored in whole autologous serum at 1° to 4° C exhibited no growth or tendency to reduce the pH of the medium after three days' storage. Material stored for shorter periods was not studied.

TABLE V—Results of Tissue Cultures on Dog Aorta Stored in Serum Ultrafiltrate and Serum Ultrafiltrate with 10% Serum and BSS. Medium-sized Pieces of Tissue Were Stored

Storage Medium	Storage Temperature	Storage Time	Percentage of Pieces Growing	
			Cotton stoppered	Rubber stoppered
Serum ultra filtrate	1°–4° C	14 days	75	
		17	87.5	100
		29	62.5	
		44	25	
		57	0	
Serum ultra filtrate with 10% serum and BSS	6°–11° C	17	100	100
		33		100
	1°–4° C	14 days	62.5	
		17	100	100
		29	50	
		33	25	87.5
		44	37.5	
		57	12.5	
	6°–11° C	17	100	100
		33		25

Each percentage represents studies on 8 pieces of tissue.

V Vessels Preserved in Serum Ultrafiltrate

In general, dog vessels preserved in serum ultrafiltrate or serum ultrafiltrate plus 10 per cent serum showed growth roughly comparable to that obtained when 10 per cent serum in BSS was employed. The series of experiments was small and there were a number of variations but the impression was obtained that storage in 10 per cent serum in BSS was a little better. The addition of 10 per cent serum in BSS to the serum ultrafiltrate did not appear appreciably to improve growth. As with the earlier studies, however, sealing the flasks with rubber stoppers led to a distinct improvement in

viability of the stored tissue. The effect of the higher temperature, 6° to 11° C was again to produce more luxuriant growth at about two weeks but little difference at four or five weeks. pH changes were comparable to those encountered with 10 per cent serum in BSS but the solutions tended to remain more alkaline. The results are compared in Table V.

VI Vessels Preserved by Freezing

Material stored at -76° C showed positive growth on tissue-culture in only two of 34 experiments*. In one instance the tissue was frozen rapidly (Method B) and in another it was frozen slowly (Method C). The growth was poor in both instances. Of 12 dogs who received frozen aortic grafts, all but two died because of thrombosis or breakdown of the graft. The tissue appeared to be more friable and more difficult to suture than fresh tissue. These results are unlike those reported by Blakemore^{2, 3} and by Hufnagel¹⁶.

DISCUSSION

Although a graft of dead bone, cartilage, or blood vessel, may provide a suitable framework and produce a functional result^{12, 13, 19, 20} the evidence at hand indicates that in the case of arteries, at least, more reliable results are obtained when living tissue is employed. Consequently, efforts have been directed primarily to finding a method of preserving vessels in a viable state. Several modes of storage including freezing, have been abandoned by us at least temporarily, since when employed, viability could be demonstrated only sporadically and, in experimental animals results from grafts were poor. The method of storage recommended in this paper is not entirely new but is based on the previous work of many others.

Bert¹ refrigerated rats' tails in confined air at about +12° C for several days and then successfully transplanted them. Carrel^{6, 8} stored blood vessels, skin, fascia, and other tissues in vaseline, moist air, normal saline, and "Ringer's" solution at temperatures slightly above freezing. He evaluated his method of preservation after one to six days by cultivation of stored embryonic tissue and after intervals as long as seven weeks by grafting stored adult tissue in animals. The maximum duration of cell viability was not determined. Lambert¹⁷, Lewis and McCoy,²² Hetherington and Craig,¹⁵ Waterman,^{32, 33} Walter *et al*,³¹ Hanks and Wallace,¹⁴ Garry,¹⁰ and Carpenter,⁵ studied the survival of refrigerated embryonic and other tissues by tissue cultivation or oxygen consumption, but were either unable to demonstrate viability after more than short intervals or were concerned with comparatively brief periods of storage. Their work indicates that refrigerated tissue retains its viability for varying periods of time, depending primarily on the type of tissue,^{32, 33} and secondarily on the size of tissue pieces,²² available oxygen,^{10, 14, 24} storage temperature,^{15, 22, 33} and other factors. Irreversible changes took place quickly

* Tissue refrigerated but not frozen in the copper tubes grew well on tissue-culture, indicating that the presence of the metal itself did not account for the failure of the frozen tissues to grow.

in brain, kidney, liver, and other solid organs, while bone, cartilage, skin, fascia, and blood vessels, survived for comparatively long intervals. The degree of preservation was more or less dependent on the size of the fragments, very small pieces of tissue surviving for only brief periods. Oxygen demand was greatly diminished as the temperature fell. Tissue fragments at 37°C required very high oxygen tensions to prevent necrosis,²⁴ while at 0°C tissues were able to survive for a time even when oxygen was excluded^{10, 14}

Tissues for clinical grafting have been stored refrigerated for short intervals. La Roe¹⁸ kept skin in "Tyrode's" solution for periods of one week, while Castroviejo⁹ stored corneas for two to five days in "Ringer's" or normal saline. Both reported satisfactory clinical results. More recently, Matthews²³ preserved human skin wrapped in saline sponges, in air-tight containers at $+3^{\circ}$ to 6°C . He reported viability after eight days as measured by tissue cultivation, and stated that autogenous grafts at three months were successful.

It is thus clear that certain tissues can be preserved vitally by simple refrigeration. However, evidence concerning the limitations of storage methods is slowly accumulating. Skin¹⁴ and blood vessels (present report) can be preserved alive for about a week in the absence of a buffered environment by storing at 0°C with the exclusion of oxygen. As shown both by these workers and ourselves, however, there is an unfavorable accumulation of acid metabolites and a rapidly falling viability. Tissue stored in such media as balanced salt solution, Ringer's solution, or normal saline, at temperatures just above 0°C , will also remain alive for short periods, as demonstrated by our data, but the lack of suitable nutrient material is evidently unfavorable for lengthy preservation of viability. In addition, blood vessels so kept may become edematous and prove unsuitable for vascular grafts after as little as 24 hours' storage.¹¹ Preservation in serum or whole blood is also satisfactory for short periods of time,¹⁴ but the large protein and fat molecules seem seriously to interfere with metabolism.²⁹ The preservation of tissue in 100 per cent serum was unsuccessful in one series of experiments performed by us.

Thus, it appears that an ideal storage medium should contain a physiological concentration of salts, buffer, glucose, and the small accessory molecules which are present in serum. The large protein and fat molecules should probably be in reduced concentration. The storage medium developed by Hanks and Wallace¹⁴ fulfills these criteria. It was found by them to be entirely suitable for storage of rabbit skin for periods up to two weeks at 8°C . Their procedure was modified in our hands by employing somewhat lower temperatures and by the more liberal use of storage medium.

The use of serum ultrafiltrate as a storage medium is suggested by the above reasoning, since all of the large molecules have been removed from it, while the small molecules remain. The data accumulated to date indicates that this solution either alone or with 10 per cent serum is satisfactory but is not superior to 10 per cent serum in BSS.

In the early part of the work cotton stoppers were used in the storage flasks because we thought it was important to facilitate the metabolic exchange

of the blood vessels which was evident even at low temperatures. This proved fairly satisfactory except in the case of small vessel segments which retained viability for only relatively short periods of time.[†] Experiments conducted with tightly-stoppered flasks showed that the metabolic activity was not sufficient to require a free exchange of carbon dioxide and oxygen. In addition, it was found that small vessels preserved in this latter manner remained viable as long as did large ones. Consequently, tightly-fitting stoppers are now used routinely.

The present study indicates that blood vessels may readily be preserved alive and with normal physical properties for periods of at least seven weeks. They have been safely employed in dogs and humans during that time for homoplastic grafts. Proper exploitation of this method should improve the surgical treatment of coarctation of the aorta, Tetralogy of Fallot, arterial aneurysm, injuries to major vessels, *etc*.

The general method of storage with suitable modifications might be applicable to fascia, skin, bone, nerves, cartilage, and corneal tissue.

SUMMARY 1

The vital storage of vascular segments in 10 per cent serum and a balanced salt solution at temperatures slightly above freezing is described. The temperature of storage is not critical. The method is simple enough to be readily useful. Viability of the tissue is readily shown by growth in tissue-cultures after storage for as long as seven weeks. The preserved segments closely resemble fresh vessels in physical qualities, and a large series of successful grafts in dogs has been completed. Vessels have also been collected from humans, stored, and have been employed successfully for alleviation of the Tetralogy of Fallot and in treatment of coarctation of the aorta. This method of blood-vessel preservation appears superior to any other yet tried by us including freezing. The theoretical basis for the storage method is discussed.

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[†] It has been shown^{28, 29, 30} that a growth substance necessary for preservation as well as growth (A-factor) is destroyed or inactivated by alkaline media. Since the media in which small tissue fragments were stored frequently became more alkaline the loss of A-factor may be the explanation for their failure to grow.

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THE MEDICAL AND SURGICAL TREATMENT OF HYPERTENSION*†

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THIS PRESENTATION DEALS with the present day management of arterial hypertension as practiced by the medical and surgical staff of the Stanford University School of Medicine

In certain patients the etiology of hypertension is known, such as in the condition of coarctation of the aorta, or of cortical or medullary tumors of the adrenal gland, or renal disease including unilateral renal lesions and glomerulonephritis, but in the majority of patients the etiology of essential hypertension is not definitely known. Heinbecker's¹ humoral hypothesis, that hypofunction of the neurohypophysis sensitizes the blood vessels to a variety of pressor substances such as renin, epinephrine, and progesterone, may prove to be important. Goldblatt² has recently summarized the evidence which has led him to believe that essential hypertension is of renal origin. In general two views are currently held: some authors feel that the arteriolar vasoconstriction with resultant hypertension can be the result of increased sympathetic impulses, while others believe it may be caused by a circulating humoral substance.

In its early stages essential hypertension has no organic changes, one finds only an elevated blood pressure which varies from time to time and may exist for years or even for decades with no serious symptoms and, in some individuals, with but little shortening of life.³ In the advanced stages of this condition peripherally constricted arterioles develop that are at first functionally spastic and then later become organically damaged, manifesting such constriction by cerebral, retinal, cardiac, or renal complications. When these symptoms appear more or less simultaneously the syndrome is known clinically as malignant hypertension (usually "essential," but sometimes with a recognizable cause). Then life expectancy is brief, the majority of patients dying within two years, with an average length of life after diagnosis of about eight months.⁴

In patients with essential hypertension, as in those with peptic ulcer and probably in those suffering from angina pectoris, certain emotional and physical reactions are more intense and frequent than in healthy people of the same age. The predisposing personality of the hypertensive patient may be present in early life and is not the result of unusually high blood pressure nor

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the result of secondary vascular disease⁵ This hyperactive reaction to environmental stimuli may be of physical or endocrine origin, and once recognized can be treated by the internist with very mild sedation and by explanation to the patient of his particular reactions so that he will follow suggestions with confidence Generally the headache, dizziness and marked tenseness and nervousness can be and should be treated by removal of "environmental difficulties or adjustments to them,"⁵ supplemented by suggestion and by sedation

Even a brief survey of the published results after sympathectomy for hypertension reveals a lack of agreement regarding the selection of cases At one extreme are those who would operate upon symptom-free youths with diastolic levels of 90-100 mm Hg, in the hope that future progress of the disease will be prevented The most contradictory view is held by those who recommend operative procedures only for patients with the very worst malignant hypertension, refractory to medical management We subscribe to neither philosophy not to the former, because we as well as many others have seen patients with essential hypertension who have continued in their work without persistent symptoms for 20 and 30 years before organic changes in the arterioles have led to trouble, and because we have seen hypertensive disease progress despite sympathectomy done early in youth, not to the latter, for then operative risks are great and results unsatisfactory in actual experience In our intermediate position, sympathectomy is recommended when danger signals appear in the patient with high diastolic pressure levels when his pressure rises even higher, when his symptoms become very severe, and especially when vascular complications (particularly those threatening the eyes) become demonstrable Ignoring most of the published contraindications, we have recommended and performed operations with no arbitrary age limit and in spite of cerebral and coronary arterial occlusions, recent congestive heart failure, and even chronic glomerulonephritis It appears that our patients have in general been subject to much more severe hypertensive disease than those described by most authors

"Sympathectomy is a palliative and not a curative measure Helpful and even life saving though sympathectomy is to some patients, at present it fills only a small gap in the great therapeutic problems of essential hypertension"⁶ We agree with these words of Fishberg and with his estimate that sympathectomy and splanchnicectomy are indicated in only a very small proportion of patients with essential hypertension⁶

Special attention will be given elsewhere⁷ to the chronic glomerulonephritic patient with hypertension Although usually considered as too bad risks for surgery and thought not to respond, a few patients with advanced renal disease with azotemia have been operated upon with results considered worthwhile since they received relief from incapacitating and intolerable symptoms Ten such patients had the one stage bilateral transdiaphragmatic splanchnicectomy and sympathectomy Two could not be followed after operation and one died in the immediate postoperative period Of the re-

maining seven, two died from uremia after five and eight months of freedom from their severe preoperative symptoms and the other five patients have remained asymptomatic for periods ranging from three to 49 months

The surgical experience with splanchnic and sympathetic resection for severe hypertension and vascular damage in approximately 130 patients in this report extends over 13 years beginning in 1935. We have realized throughout this period that we were attempting surgically to help a symptom, namely high blood pressure, and were in no way seeking a cure of the cause of hypertension

Our operative procedure has always been one stage with two operators working simultaneously, since the unilateral operation has very little effect upon the blood pressure. The one-stage operation, lasting a little over an hour, always is easier on the patient, because there is not the waiting period nor the hazard of a second operation and a second anesthesia. The Peet⁸ procedure of supradiaphragmatic resection was done until February 1942 when a modification of the Smithwick⁹ operation was developed. In some recent cases with rapidly failing vision, retinal hemorrhage and papilloedema, bilateral sympathetic denervation of the head by removal of T₂ and T₃ sympathetic ganglia through a separate transverse incision has been done at the beginning of the bilateral thoracolumbar resection

The results in the first 40 patients operated upon from 1935 to 1938 by the Peet procedure have been published in 1940.¹⁰ We now wish to present the status of these same patients as determined in 1947-1948. There was a 20 per cent mortality within the first two weeks chiefly through failure to maintain adequate operative and postoperative arterial pressure. (It was about 1940 that neosynephrine was first used routinely to prevent renal and cerebral ischemia.) Sixteen patients (40 per cent) died of hypertensive disease in from two weeks to two years after operation, only three or four of these had even transient symptomatic improvement. Five patients (12.5 per cent) could not be traced and of these three or four are probably dead, four had shown no postoperative improvement up to five years, and one patient's headaches were relieved but his pressure levels had already exceeded the postoperative maximum 20 months after operation, beyond which time he could not be followed. Six additional patients (15 per cent) are known to have died of hypertensive disease four, six, six, ten, ten, and 11 years after operation, some following shorter periods of symptomatic improvement, three of these were included in the group with the best results, including an appreciable fall of blood pressure, when the first postoperative study¹⁰ was made.

Only five patients (12.5 per cent) are known to be living, at 9-12 years after operation. In each, the blood pressure is now at or above the preoperative level. One of these (Mrs. G. in Table 3 of reference 10) had never shown improvement, in one (Case 4 of reference 10) the symptoms of fulness in the head and markedly pulsating arteries were alleviated without reduction of pressure, in three (Cases 6-8 of reference 10) objective improvement had been found for several years.

Neither enough time had elapsed nor adequate data acquired to warrant a report on all of the remaining patients. Without further conscious selection, however, the present state of fifty patients operated upon from 1938 to 1946 may be given*. There were only three postoperative deaths (6 per cent), but 21 others (42 per cent) died of their disease between two weeks and two years after operation. An additional six (12 per cent) died of hypertensive complications about four years postoperatively. Nine (18 per cent) appeared

TABLE I—*Results of Splanchnic and Sympathetic Resections in Ninety Hypertensive Patients*

Status in	40 Operations 1935-1938	50 Operations 1938-1946	
	1940 Per Cent	1947-48 Per Cent	1947-48 Per Cent
Died in 2 weeks	20	20	6
Died in 2 years	27	40	42
Died later		15	12
Not followed		12.5	
Unchanged	23	25	18
Symptomatic improvement	15	10	18
Pressure reduced	15	0	4

to be unchanged, and an equal number obtained symptomatic but not objective relief. In only two patients (4 per cent) does the pressure remain appreciably lower, after one and one-half and six years. This is not the entire story, rehabilitation and fall in pressure levels were very gratifying in three patients (6 per cent) for two to four years prior to relapse, with subsequent death in two.

Table I outlines the above findings briefly. If statistics as a whole mean anything, these results may seem not to compare favorably with those of others. We wish to point out again, however, that the patients selected for operation generally suffered more hypertensive disease than those usually described by other authors.

For the type of patient referred to us for resection we feel the operative procedure is adequate and that total sympathectomy would not alter the statistics as presented. We are in accord with Heinbecker¹¹ that probably "the only two organs capable of releasing humors concerned with the pathogenesis and symptomatology of hypertension and whose function can be modified by sympathectomy are the kidneys and the adrenals." Anatomic studies of the innervation of the kidney and adrenal glands show that the nerves pass from the celiac ganglion and the upper two lumbar ganglia so that removal of the splanchnic nerves and the sympathetic chain from T₉ or T₁₀ through L₂ ganglia should effectively denervate the kidneys and adrenals.

We have modified the Smithwick operation by extending the Pect ap proach. Bilateral paravertebral incisions are made by two surgeons working as a team and the operation is carried out simultaneously on both sides (Fig

* More than 80 per cent of the operations were performed in 1941-1945

1) The long back musculature is divided and segments of the 11th and 12th ribs are resected from the transverse processes laterally for 4 to 5 cm (Fig 2) The intercostal muscle bundle and vessels are resected leaving the intercostal nerve intact as the long brain spatulae are now used for retracting the pleura without trauma to the nerve (Fig 3) The pleura is pushed away from the vertebral bodies. The outer crus of the diaphragm is pushed off or separated

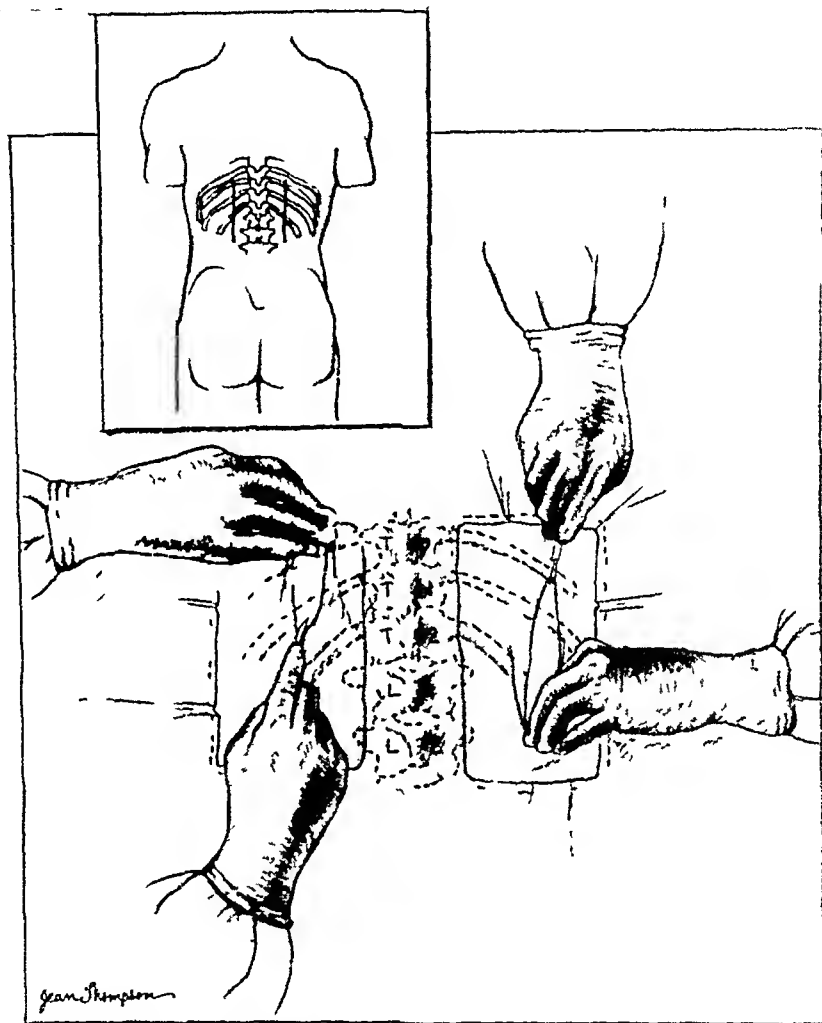


FIG 1—Position of patient, and of incisions being made by two operators working simultaneously in performing the one stage bilateral transdiaphragmatic splanchnicectomy and sympathectomy

from the body of the 1st lumbar vertebra and the diaphragm is split in the direction of its fibers for 3 to 4 cm for palpation and if necessary inspection of the adrenals and upper poles of the kidneys. The retropleural space is freed upward to the level of the 8th or 9th rib and the sympathetic chain, splanchnic nerves and the branches to the aorta on the left side are mobilized (Fig 4) The sympathetic fibers are followed downward in the retroperitoneal space until the 2nd lumbar sympathetic ganglion is located. The chain is divided below this ganglion and then above, usually between the 8th and 9th thoracic ganglia. The greater and lesser splanchnic nerves are resected from the 8th

or 9th rib down to and including the upper half of the celiac ganglion. Ordinarily the patient receives 500 cc of whole blood during the operation. Neosynephrine is administered by the anesthetist as it is necessary to maintain at all times an adequate blood pressure during and following the operation, using 0.1 cc intravenously or 0.2 to 0.4 cc intramuscularly of a 1:1000 solution.

The blood pressure may fall precipitously to dangerous levels during and

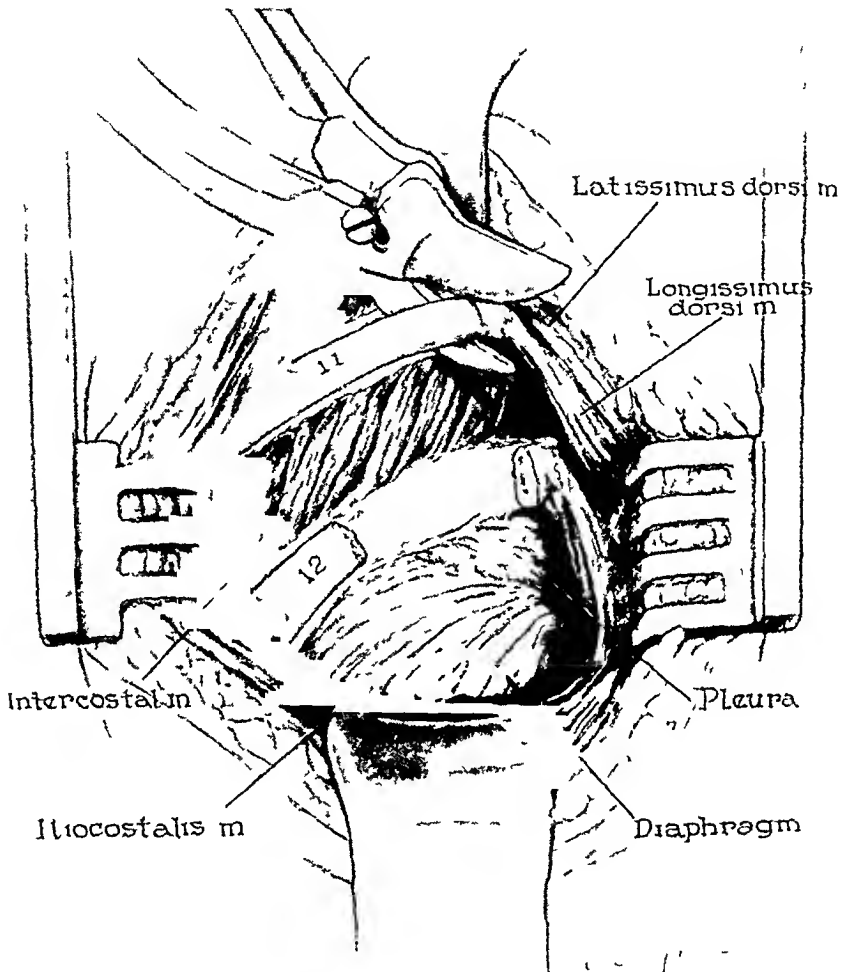


FIG 2—Exposure of 11th and 12th ribs, pleura and diaphragm with resection of the inner portions with transverse processes of 11th and 12th ribs

after a one stage splanchnicectomy and sympathectomy if special efforts to maintain it are not employed. Shock, cerebral anoxia, and renal ischemia are the principal dangers, the latter complications being of particular importance in patients with advanced renal disease. Blood pressure measurements are made every 5 to 15 minutes during the first postoperative day and less frequently thereafter as is indicated. If the blood pressure falls below 140 over 100, neosynephrine is administered. It may be necessary at times to continuously infuse neosynephrine diluted with 5 per cent glucose in distilled water.

HYPERTENSION

Maintenance of an adequate fluid balance is necessary and is of the utmost importance in patients with advanced renal disease and azotemia. If dehydration and salt depletion occur it may be difficult to sustain the blood pressure at desired levels, the azotemia may be intensified and acidosis may ensue. Administration of excess salt and water may result in edema and heart failure.

The 24-hour urine volume and quantity of sodium chloride excreted is measured daily in those patients with severe renal lesions. The total fluid

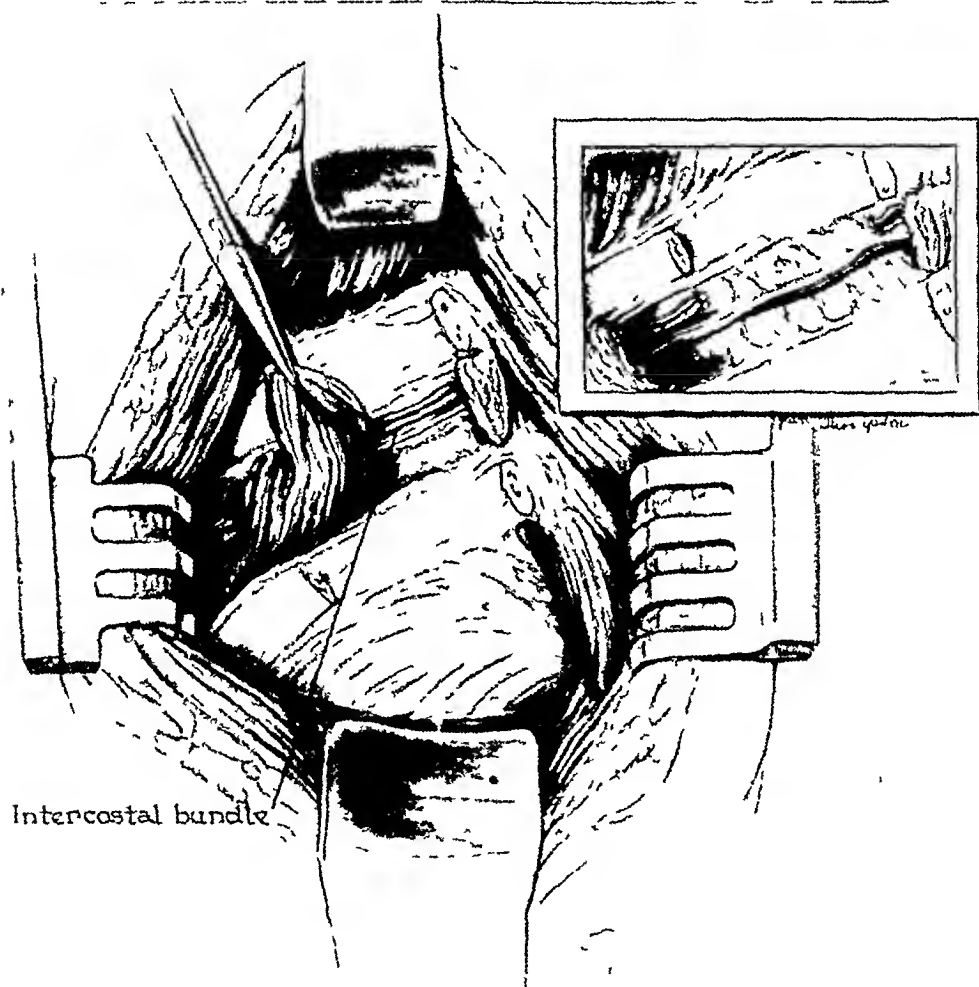


FIG 3—Removal of muscle and vascular bundles between beds of 11th and 12 ribs leaving 11th intercostal nerve intact

intake and output is also measured. Fluids should be given slowly and cautiously, usually about 2000 cc daily in excess of that lost by vomiting. Since little or no salt is lost in the urine, only enough to replace that lost by sweating and vomiting is needed.

Unless an adequate number of calories is supplied, body protein will be used for energy, deamination of amino acids will be increased, and the azotemia may be intensified. Intravenous solutions should contain glucose of 5 to 10

per cent, the patient should be urged to consume food and fruit juices with sugar as early as possible after operation. When food can be eaten without difficulty, an adequate low protein diet is given.

Following operation intercostal neuralgia of varying degree develops even if the intercostal nerves are divided. Seconal and nembutal are of help for this condition which lasts from one to several weeks and causes fluctuation in the postoperative blood pressure.

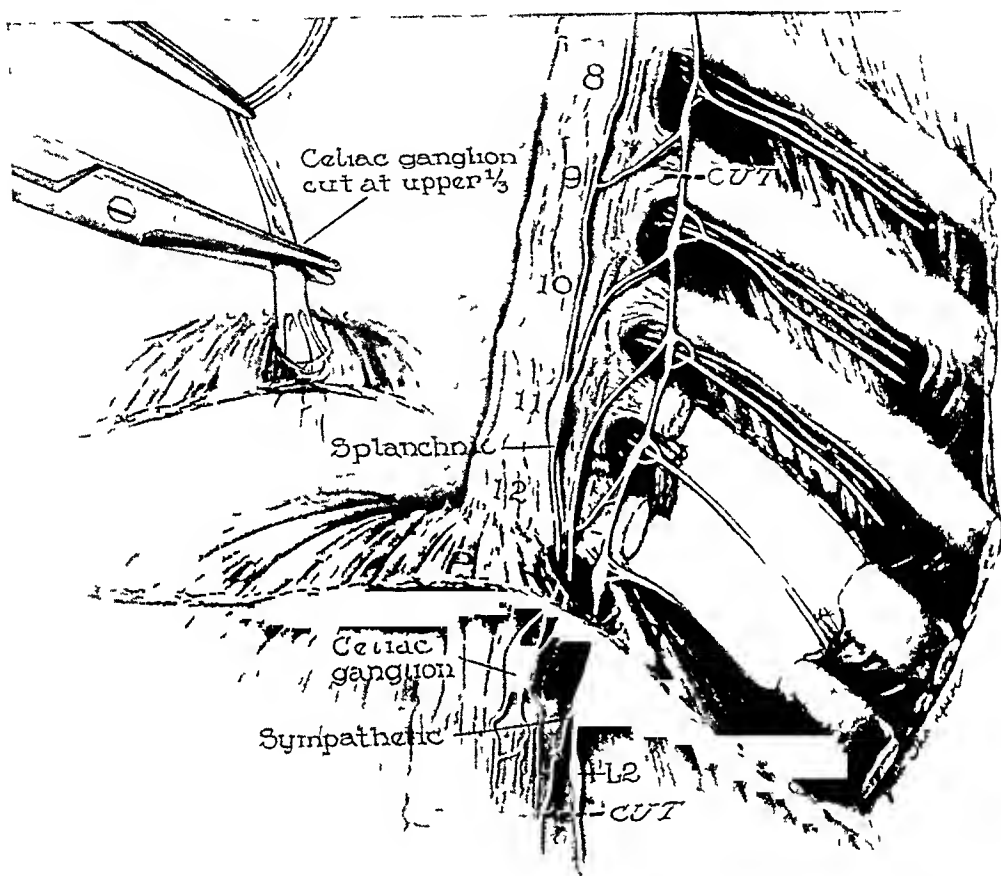


FIG 4—Diaphragmatic representation of the position of and the amount removed of the splanchnic and sympathetic nerves in the one stage bilateral thoracolumbar splanchnicectomy and sympathectomy

Usually in the second week when tension has subsided the patient's mode of life and work is discussed and adjustments planned not only with the patient but with his or her family. The proper reaction of the patient to the environment is most important in seeking a successful outcome from the operation, and the surgeon should be of great aid to the internist in securing this adjustment. We are in accord however with Ayman's⁵ statement that essential hypertension still is a medical disease which should be studied primarily by the internist whose experience is obviously much greater than that of the surgeon in the evaluation of cerebral, cardiac, and renal functions. The post-operative evaluation should also be primarily in the hands of the internist.

SUMMARY

Essential hypertension is fundamentally a disease which in the great majority of our patients has been adequately treated for years and for decades by the internists of the Stanford University School of Medicine

After long medical treatment certain few patients no longer respond favorably because of the development of malignant hypertension, or because of renal, cerebral or cardiac complications of essential hypertension, or because the glomerulonephritic case with hypertension enters into the terminal stages

Such patients, although considered unsatisfactory for operation by most surgeons, are recommended for the one stage bilateral transdiaphragmatic splanchnic and sympathetic trunk resection in which procedure two surgeons operate simultaneously

With proper operative and postoperative attention to maintenance of an adequate blood pressure at all times, the immediate mortality has been about 6 per cent

Such patients referred for operation are given continued and careful supervision by the internist immediately after the operation to prevent cerebral anoxia and renal failure

This operative procedure affords a minimal surgical strain on such patients and is considered worth while because it offers temporary symptomatic relief in about one-fifth of the referred cases

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CONTROL OF HEMORRHAGE FROM WOUNDS OF THE CORONARY VESSELS BY THE GELATIN SPONGE PATCH TECHNIC*†

An Experimental Study

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THE ABSORPTION¹ and hemostatic action² of gelatin sponge has been the subject of several previous communications. In experimental resections of the liver the control of hemorrhage with gelatin sponge has been obtained by the "blanket" technic and in wounds of large veins by the "patch" method³. In experimental wounds of large arteries the hemorrhage has been controlled by a "cuff" of dry compressed gelatin sponge supported by a chromic catgut sheath⁴. In experimental wounds of the auricles⁵ and ventricles⁶ the gelatin sponge "patch" was found adequate to control massive hemorrhage from the heart.

The application of these experimental studies to the problems of hemostasis in general surgery has been outlined⁷ and clinical observations on the use of gelatin sponge in patients has been presented^{2, 8, 9}. It has been pointed out that the indications for the use of gelatin sponge or any other hemostatic agent in clinical surgery should be limited to the control of hemorrhage where ligature or suture was not adequate, desirable, or feasible.

Hemorrhage from wounds of coronary vessels appeared to present a particular challenge in hemostasis, in that the vessels are too small and in too rapid motion to permit suture of the wound and the sequel of myocardial infarction too hazardous to permit ligation of the vessels, especially the artery. Although hemorrhage from wounds of the coronary vessels may be encountered rather infrequently, nevertheless they do occasionally occur as a result of trauma, pericardiocentesis, or in the course of a pericardiectomy.

This experimental study was undertaken to determine the feasibility of utilizing the gelatin sponge "patch" technic to meet this particular clinical problem of hemostasis, as well as to evaluate the effectiveness of this hemostatic agent by a more critical experimental test than has heretofore been carried out.

EXPERIMENT

The dogs were anesthetized with Nembutal using 33 mg per kilogram of body weight. A tube connected with an adjustable positive pressure air valve

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† This work was aided by a grant from the Upjohn Company, to the University of Illinois College of Medicine

was introduced into the trachea. With aseptic technic, an incision was made on the left side of the thorax entering the pleural cavity in the 4th interspace. The degree of lung expansion was regulated by immersing the air outlet tube from the closed mask in a 5 gallon jug of water. The pericardium was opened and special care was taken to avoid torsion and kinking of the base of the heart. A wound was made with a scalpel in the anterior descending branch of the left coronary artery and vein producing a copious hemorrhage which had enough force to carry the stream of blood 3 to 4 feet. (See Fig 1.) It is believed that in some instances the scalpel wound completely transected



FIG 1—Showing hemorrhage from scalpel wound of coronary artery and vein. A—incision in wall of artery and vein. B—the massive spurt of blood through the incision. C—tip of auricle.

the artery, although in most instances a partial transection was undoubtedly obtained. In the first five experiments the wound was made in one of the major terminal branches. In the remainder of the experiments the wound was placed proximal to the major terminal bifurcation in the upper third of the artery just medial to the tip of the left auricle. The "patch" of gelatin sponge was prepared from the commercially available product "Gelfoam" size 100 which is provided sterile in sealed packages. The gelatin sponge was first compressed by the fingers and then a piece about 1 inch square cut out of the larger compressed sheet. These "patches" of dry compressed gelatin sponge

were applied over the bleeding wound in the vessels and held in place with the fingers for 10 to 20 minutes. In most instances it was found necessary to use as many as four or five successive patches before the hemorrhage was completely controlled. An additional reinforcing patch was usually necessary. In using the dry compressed gelatin sponge there is a tendency for the sponge to stick to the gloves, so that in removing the finger pressure from the patch, dislodgment occurs. This was obviated in these experiments by first letting one side of the sponge become soaked in blood and then turning it over, using pressure of the gloved fingers on the outer blood soaked side.

The gelatin sponge patch technic was used in 37 experiments in which wounds were produced in the coronary artery and vein. In four other control experiments oxidized cellulose was used. In addition there was a control series of two animals in which the coronary vessels were ligated after transection. In two animals a blood soaked gelatin sponge patch was inserted into the pericardial cavity without producing a wound of the vessel. These latter two experiments were done as controls for the electrocardiographic studies which were made on most of the animals before, during, and after the wound of the vessel was produced or the vessels ligated.

The animals which survived the experiment were sacrificed at varying periods of time from one week to six months after the wound was produced. Photographs were taken of the heart and arteriograms were made of the left coronary artery, using either red lead or metallic mercury. Several of the hearts were prepared as cleared tissue specimens and in the remainder the area where the wound had been produced was cut out and prepared for microscopic study.

RESULTS

In the series of 37 experiments in which a gelatin sponge patch was used as the method of attempting control of hemorrhage from scalpel wounds of the anterior descending branch of the left coronary artery and vein, the following results were obtained:

In three experiments, ventricular fibrillation and cardiac arrest occurred before the hemorrhage could be controlled by the gelatin sponge patch. In one of these, death occurred shortly after the wound was made in the vessels. In two experiments death occurred 35 minutes to one hour afterwards, and represents a definite failure to obtain hemostasis by this method.

In four experiments, the hemorrhage was controlled by the gelatin sponge patch but ventricular fibrillation and cardiac arrest occurred shortly afterwards. In two this occurred before closing the pericardium, in one it occurred while the chest wound was being closed, and in one other it occurred after the chest was closed, the fibrillation being detected by the electrocardiogram. On reopening the chest this was substantiated and attempts at defibrillation failed.

In one experiment, the hemorrhage was controlled by the patch but the animal died shortly after the chest was closed, apparently as a result of the anesthesia.

HEMORRHAGE IN CORONARY WOUNDS

In two experiments, the animal died some time during the night after the operation and at autopsy were found to have a hemopericardium due to dislodgment of the patch and secondary hemorrhage



FIG 2—Showing gelatin sponge patch covering wound of the coronary vessels. The control of the hemorrhage is apparently due to the clotting of the blood in the interstices of the sponge which produces essentially a "reinforced clot," the gelatin sponge furnishing the structural support. This "reinforced clot" seals off the wound in the vessel, prevents further loss of blood, and permits restoration of blood flow in most instances until healing occurs

In one experiment, the animal died some time during the night after the operation and at autopsy 20 cc of blood was found in the pericardial cavity, although the sponge was adherent to the wound in the coronary vessels. This

amount of hemopericardium may have contributed to the impairment of cardiac function but did not seem to be the sole cause of death, which was probably due to myocardial changes as a result of impairment of circulation after cutting the vessels



FIG 3—Showing gelatin sponge patch one week after application to wound of coronary vessels. The patch is moderately adherent to the visceral and parietal pericardium and firmly adherent to the area where the wound was produced

In 26 experiments, the hemorrhage from the wound in the coronary vessels was controlled by the gelatin sponge patch technic and the animals survived the experiment (See Fig 2). The number of patches required to obtain hemostasis varied from one to nine and usually at least one reinforcing patch was necessary. In most of the experiments at least four or five successive patches

were used before the bleeding was adequately controlled by a final reinforcing patch

One animal died after two days from pneumonia and one after a week as a result of massive infection in the chest incision. The remaining 24 animals were sacrificed at varying periods of time from one week to six months after



FIG 4—Showing gelatin sponge patch six weeks after application to wound of coronary vessels. The patch has thinned out considerably due to absorption and is so adherent to the heart that it cannot be removed except by sharp dissection

the wound was produced. The length of time before sacrificing was as follows: two at one week, two at two weeks, two at three weeks, one at four weeks, one at six weeks, three at two months, two at two and one-half months, five between two and one-half and three months, two at three months, one each at three and one-half, four and one-half, five and six months.

The condition of the gelatin sponge at autopsy varied according to the length of time it had been implanted. During the first few weeks the sponge was red in color and became increasingly firm. It was only moderately attached to the visceral pericardium during the first week by thin transparent fibrinous adhesions as well as to the parietal pericardium. The sponge remained rather firmly adherent, however, to the area where the wound was

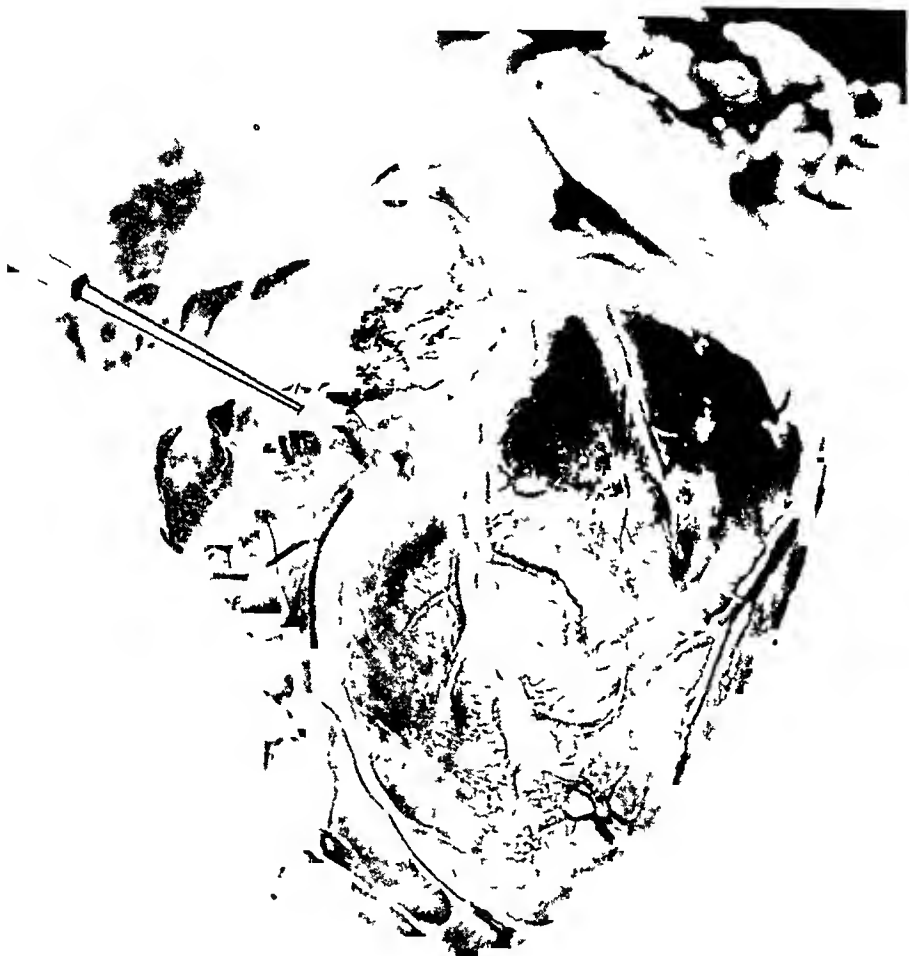


FIG 5—Showing condition of coronary vessels 12 weeks after patch of gelatin sponge applied to wound. The gelatin sponge has been completely absorbed and replaced by a small fibrous plaque which covers the area where the wound was produced. Arteriogram demonstrates patency where the wound was produced.

made and could not be separated from this region without tearing the sponge. After one week the sponge became increasingly adherent to the visceral as well as parietal pericardium (See Fig 3) and after three weeks the sponge tended to split when the pericardial sac was removed, leaving a portion of the sponge adherent to both structures. After four weeks the sponge became somewhat translucent, took on a tan color, and had a glazed appearance and could not be

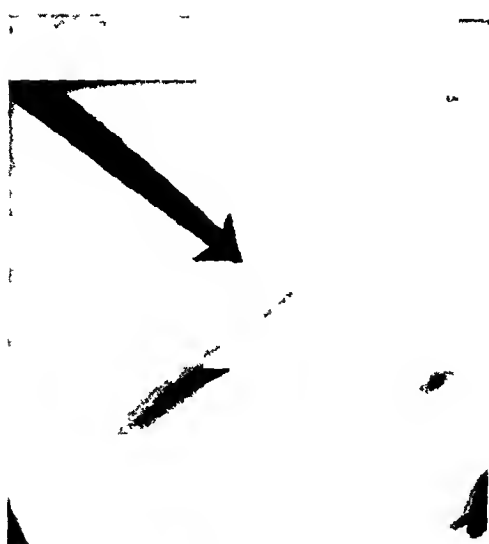
separated from the heart except by sharp dissection. After six weeks the gelatin sponge patch was considerably thinned out (See Fig 4). After eight weeks the sponge was completely absorbed as far as one could determine from the gross appearance. In place of the sponge there was a fibrous plaque which was considerably smaller than the original sponge and which could be separated from the pericardium only by sharp dissection (See Fig 5). After ten weeks this fibrous plaque became somewhat transparent and the wound in the coronary vessels could be identified as a thin transverse scar. After three months or more this fibrous plaque became so small that it was often difficult to identify the area where the wound in the vessel had been produced.

Evidence of myocardial infarction was observed in only two of the specimens examined. The patency of the coronary artery was determined by arteriography using either an aqueous suspension of red lead or metallic mercury. The former gave better detail in the terminal arterioles, but the mercury gave better contrast of the vessel at the site of the wound. In most of the specimens there was no demonstrable interruption of the opaque medium on roentgen ray, indicating patency of the vessel at the point of injury. Evidence of a constriction or a tortuosity of the vessel at the site of the wound was demonstrated in two dogs. A definite filling defect was observed in three specimens at the level of the wound which indicated obliteration of the vessel for approximately 1 cm (See Fig 6 showing arteriograms). In only one of these was there gross evidence of an infarct. The other infarct was found in a specimen where the arteriogram demonstrated a tortuous lumen of the vessel at the site of injury.

Control Series—In four experiments oxidized gauze was used in an attempt to control hemorrhage from the wounds of the coronary vessels. When two, four, or six layers of the oxidized gauze were used over the bleeding vessel it was found that the bleeding continued through the interstices of the gauze. With eight layers of gauze it was possible to control the hemorrhage as long as finger pressure was maintained on the gauze. However, it was found that the gauze would not adhere to the heart sufficiently well after removal of the pressure of the finger to maintain control of the hemorrhage. Furthermore the oxidized gauze became rather firm after it had been soaked in blood while pressure was being maintained and even if it did adhere to the heart it would not expand and contract with the heart muscle as the gelatin sponge was found to do.

In two experiments the anterior descending branch of the left coronary artery and vein was doubly ligated and transected between the ligatures. Within five minutes there was evidence of cyanosis of the heart muscle distal to the ligature. Within 20 minutes the electrocardiographic changes were rather striking. After two weeks a definite infarct of the anterior wall was found. In one animal the entire anterior wall including the apex was involved. This dog died suddenly after eating a hearty meal two weeks after the ligation was done. The other animal which was sacrificed after two weeks had a large infarct of

A



B

C

FIG 6—Showing arteriograms of specimens (metallic mercury in left coronary)

A No evidence of constriction, dilatation, or deformity of the vessel where wound was produced 6 months previously (indicated by pointer) Most of the arteriograms were similar to this

B Constriction and irregularity of the lumen of the coronary artery where the wound was produced 3 months previously, but no evidence of occlusion of the vessel at this time One other arteriogram was similar to this

C Interruption of opaque medium at point where wound was made 3½ months previously indicating obliteration of the lumen Two other arteriograms were comparable to this In one of these there was a gross infarct

the anterior wall Although two infarcts were observed in the series in which the vessels were cut with a scalpel, the lesions were not of this magnitude

Electrocardiography—Electrocardiograms were taken before, during the course of the operation when the wound of the coronary vessel was produced, or the vessel ligated, and after the operation, the classical limb lead and the

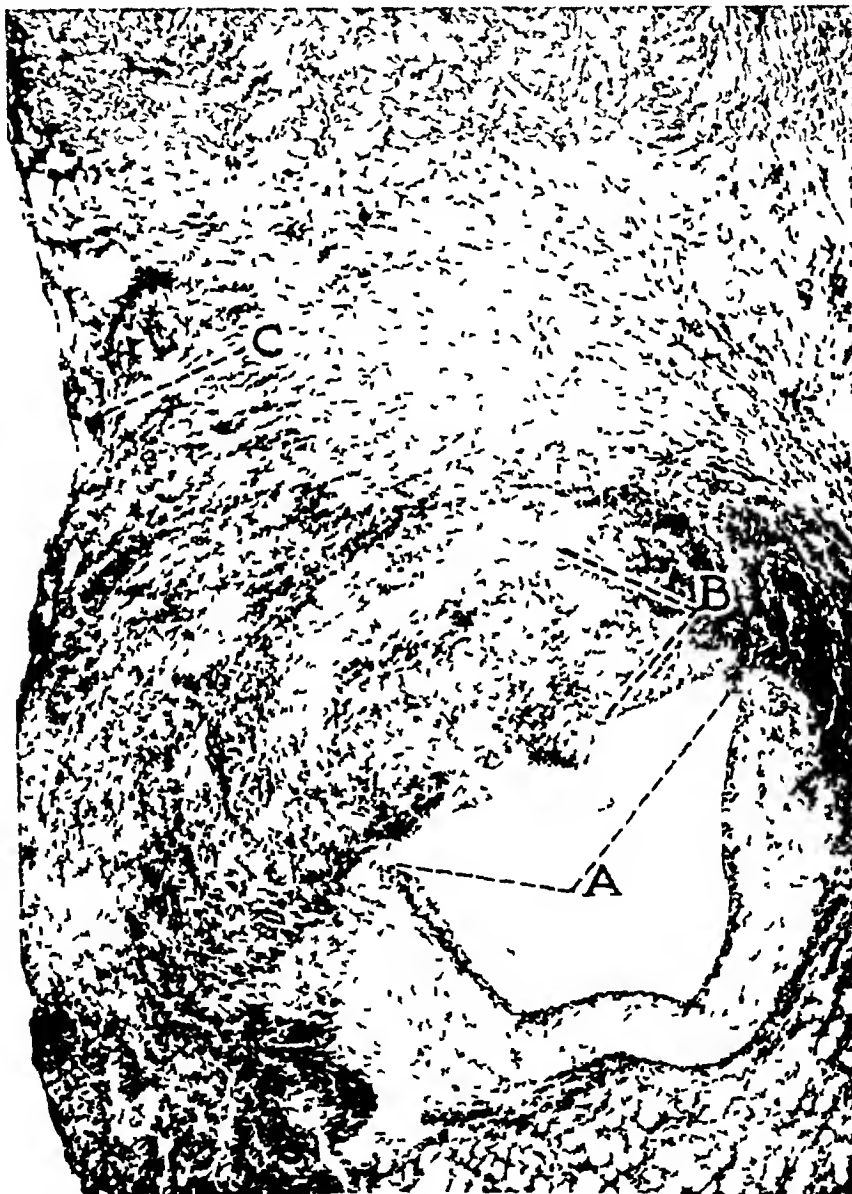


FIG 7—Showing photomicrographs of wound of coronary artery
after eight days
A—defect in wall of artery
B—organizing hematoma lined by endothelium
C—fragment of gelatin sponge

chest leads (LI, II, III, CR, CF, CL, and V) were used The chest lead was static, one interspace below the PMI to avoid the line of incision Since dog electrocardiograms are exceedingly variable, each dog's preoperative tracing was used as the control for that animal Generalized normals were not used

At the time of incision of the coronary vessels Lead III showed a ventricular extrasystole and during the period of bleeding showers of extrasystoles sometimes occurred, followed by the resumption of a normal rhythm and contraction sequence

In those animals in which there was no gross infarct following incision of the coronary artery, the electrocardiographic changes involved the ST segments and the T waves. There were no significant early changes in the QRS waves. Acutely, and persisting, there was depression of the ST segments and inversion of the T wave. ST changes of similar character were noted in sponge control dogs. Later, T₂ and T₃ were deformed, becoming diphasic and notched and a Q of significant amplitude appeared in Lead II.

In dogs which had a demonstrable gross infarct after incision of the coronary artery (two experiments) and in the two experiments in which the coronary artery was ligated, the electrocardiograph changes resembled those generally found in infarction of the myocardium, *i.e.*, acute elevation of the ST segment and inversion of the T wave with evolution in subsequent electrocardiograms following the usual pattern of myocardial infarction.

Microscopic Study—The microscopic study of the coronary vessels was carried out with sections, most of which were cut across the vessel, while some were cut longitudinally. It was necessary to prepare a large number of serial sections to locate the wound in the artery because in many instances it was difficult to determine grossly just where the wound had been produced. One of the most interesting points in this microscopic study was the observation that the wound in the vessel was rather rapidly repaired by endothelialization of newly formed scar tissue (see Fig 7) under the gelatin sponge patch. In two instances the wound communicated with a small aneurysmal sac which was not previously visualized by the arteriogram. In one instance the serial sections revealed an endothelialized vascular channel through an area of fibroplasia and organizing hematoma which probably represented a small defect between the ends of the transected artery. Later, there was a well formed scar lined by endothelium which sealed off the wound (See Fig 8). In some instances a small outpouching of the lumen could be seen in this scar.

The behavior of the gelatin sponge in the tissues was essentially the same as described previously. There was invasion of the sponge by fibroblasts, deposits of collagen in the sponge, gradual absorption of the sponge by the action of macrophages, and ultimate absorption of the sponge in about two months leaving a small fibrous tissue plaque where the sponge had sealed off the wound in the artery.

COMMENT

The control of hemorrhage from wounds of the coronary artery and vein in experimental animals by a non-suture method—the gelatin sponge “patch”—is of some significance from the standpoint of its possible clinical application where suture would not be feasible and ligation most undesirable. One should not, however, underestimate the technical problem of obtaining hemostasis

under such conditions. It is important to emphasize that a great deal of care and patience is required to obtain satisfactory results with gelatin sponge under such critical conditions. Anyone attempting to use gelatin sponge for hemorrhage of comparable magnitude in patients should spend some time familiarizing himself with the handling of this material under similar experimental conditions.



FIG 8—Showing photomicrograph of coronary artery where wound was produced three months previously

A—site of wound

B—replacement of defect in vessel wall by fibrous tissue plaque

C—endothelial lining of fibrous plaque

in animals. It should be stressed that as many as four to five successive sponges were ordinarily used in these experiments and sometimes as many as nine sponges before the massive bleeding was brought under control. Even then an additional reinforcing patch was generally necessary. The fact that it was possible to obtain control of hemorrhage from wounds of the coronary

vessels by this non-suture and non-ligature method and have the animal survive for 48 hours or more in about 70 per cent of the experiments represents a rather critical test of the effectiveness of one of the new hemostatic agents—gelatin sponge

Of the 11 experiments in which the animal died during, immediately afterwards, or some time during the night after operation, there were four which represent a definite failure of this method, two in which the hemorrhage could not be controlled and two in which there was secondary hemorrhage due to dislodgement of the patch. Of the remaining seven early deaths, most of these could be attributed in varying degree to myocardial ischemia due to cutting of the vessels or to the operative manipulation of the heart. Both of these factors lead to ventricular fibrillation. Of these seven deaths there were four in which the hemorrhage was controlled by the gelatin sponge patch before fibrillation of the heart developed.

When one takes into consideration that interruption of the coronary artery circulation by ligation at the level where the incision was made in most of these experiments has a mortality of 70 per cent,¹⁰ it is not surprising that there is an appreciable mortality to temporary interruption of the circulation such as must occur between the time the wound is produced in the vessels, and the control of the hemorrhage by the gelatin sponge patch. At least 11 per cent of those animals which died promptly after the experiment represent an unquestioned failure of this gelatin sponge patch technic. On the other hand, in 19 per cent of the experiments the early death could be attributed to a considerable extent to the operative procedure on the heart and the wound of the coronary vessels which produced enough disturbance in the cardiac physiology to bring about a lethal outcome.

Another interesting feature of this work aside from the control of hemorrhage by this "patch" method is the rapid healing of the wound in the vessel and the relatively infrequent occlusion of the vessel by thrombosis at the level of the wound. In only three specimens did the arteriogram demonstrate a complete occlusion. These were in animals which survived one week, three months and three and one-half months respectively. In one of these there was a definite infarcted area but it was smaller than that observed after ligation at this level. In two of the arteriograms there was some evidence of constriction or deformity of the vessel at the level of the wound. In one of these there was an infarction of the myocardium. It is presumed that the patency of the vessel by arteriography may represent a recanalization of the vessel after occlusion by thrombosis, which originated at the level of the wound. The relatively good healing of the wound in the vessels which were "patched" with gelatin sponge is apparently due to the rapid endothelialization of the vascular channel between the edges of the wound under the protective cover of the gelatin sponge patch.

The electrocardiographic studies in these experiments were of interest primarily from the standpoint that the characteristic changes generally seen

after coronary occlusion, and found in the ligature control series, did not occur after cutting the vessel and restoring the blood flow with the aid of the gelatin sponge patch. Such changes as did occur in the electrocardiogram following transection of the vessel resembled "strain patterns," characterized by inversion of TI, depression of ST segments, and changes in the contours of the T waves, except for the two instances where infarction occurred and in these tracings the changes were comparable to those found after ligation.

It is recognized that the interpretation of the electrocardiograms in dogs represents somewhat of a problem and a more detailed report of this phase of the work will be made subsequently. It is believed that the method of taking electrocardiograms which can be read and identified while the experiment is in progress represents a distinct advantage in work of this type. As a result of the stimulus from this experimental work, it is planned to install a visual recording electrocardiograph in the hospital operating rooms for tracings on patients especially of the older age group so that a better evaluation of the cardiac status can be obtained during the course of prolonged anesthesia for radical surgery.

The failure to obtain control of hemorrhage from wounds of the coronary vessels with oxidized cellulose is of some importance in evaluating the properties of this hemostatic agent. The use of oxidized cellulose for wounds of the *vena cava* in dogs was also found to be unsatisfactory. The principal point which was observed was that the oxidized cellulose would control the hemorrhage as long as finger pressure was maintained and if rather thick pads were used. However, there was relatively little tendency for the oxidized cellulose to adhere to the heart or the *vena cava* after the finger pressure was removed, and thus the control of hemorrhage was not maintained. This brings up the basic difference in these two hemostatic agents: the oxidized cellulose appears to act primarily as a chemical coagulating agent, whereas the gelatin sponge acts as the structural support for a blood clot. Thus, one could say that the principal indication for the use of gelatin sponge is where the control of hemorrhage can best be accomplished and maintained by a "reinforced clot." These observations do not in any way negate the value of oxidized cellulose for many of the problems of hemostasis in surgery where an absorbable coagulating medium is indicated, but rather suggest that in some types of hemorrhage the gelatin sponge may be more effective.

In these experiments on dogs, no thrombin was used in the gelatin sponge. Thrombin was omitted primarily to evaluate the effectiveness of the sponge alone. Furthermore, the thrombin may be definitely contraindicated where the gelatin sponge is used for control of hemorrhage from blood vessels as it could probably contribute to intravascular thrombosis if any of the thrombin escaped into the lumen of the vessel.

SUMMARY

In a series of 37 experiments on dogs, a scalpel wound was produced in the anterior descending branch of the left coronary artery and vein. The hemor-

rhage was controlled by the application of a gelatin sponge patch and the animal survived the immediate operative period in 70 per cent of the experiments. In 11 per cent of the experiments, this "patch" technic was a failure. In 19 per cent of the experiments the animal died from the effects of temporary interruption of the coronary circulation, manipulation of the heart or the anesthesia.

CONCLUSIONS

The gelatin sponge patch technic may provide a desirable means of controlling hemorrhage from wounds of coronary vessels and thus restoring blood flow in a vital vessel where suture may not be at all feasible and ligature not desirable. For wounds of the coronary vein alone, the "patch" technic is relatively simple, however, for wounds involving the coronary artery it is doubtful that one could expect satisfactory results in patients without previous experience with this technic in experimental animals.

The control of hemorrhage by gelatin sponge under the conditions obtaining in this experimental study represents a rather critical test of the effectiveness of this hemostatic agent.

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TOTAL GASTRECTOMY FOR CARCINOMA OF THE STOMACH*

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THE FIRST COMPLETE RESECTION of the stomach in man was performed by Phineus Conner of Cincinnati, in 1884.¹ The patient, moribund at the time of operation, died on the table and it was not until 1897, 13 years later, that Schlaetter of Zurich was able to report the first successful total gastrectomy.² This patient lived for 14 months before dying of a recurrence of the carcinoma. In 1898, four American surgeons, Brigham,³ MacDonald,⁴ Richardson,⁵ and Harvie,⁶ each successfully removed the entire stomach from patients suffering from gastric carcinoma. The patients of Brigham and MacDonald were reported to be alive and well eight and seven years respectively, after operation.⁷

In 1928, 31 years after the first successful total gastrectomy, Finney and Rienhoff⁸ reviewed the literature and found reports of 67 total gastrectomies for carcinoma. The operative mortality was 53.8 per cent. In a similar group of 55 patients subjected to radical gastrectomy, but with the preservation of 3 cm. or less of gastric wall at either the esophageal or duodenal end, there was an operative mortality of only 25 per cent. Finney and Rienhoff concluded that, "a more beneficial result clinically, physiologically, and mechanically is to be expected if one leaves a portion, ever so small, of the gastric mucosa."

By 1942 the reported number of total gastrectomies for carcinoma had risen to 298 and the operative mortality had dropped to 37.6 per cent.⁹ Of the 186 patients surviving operation only 16 or 8.5 per cent were known to have survived for more than three years. Metastatic or recurrent carcinoma was believed to be the cause of death in 82.5 per cent of the patients who survived operation but later died.

In more recent reports^{10, 11, 12, 13} the operative mortality has varied between 10 and 30 per cent, Table I, and although about half of the patients who survive operation die within a year or 18 months, approximately 20 per cent can expect to live for three years or longer.¹⁰

Studies of the nutritional status of patients who have survived total extirpation of the stomach have resulted in conflicting reports. Farris¹⁴ and associates, after studying a group of patients at the University of Michigan, stated that the stomach does not play an essential role in the digestion of fats and proteins. It was also their conclusion that while gastrectomy interferes with the metabolism of iron, primary anemias are rarely encountered. In the

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same year, 1943, Rekers¹⁵ and associates in reporting the results of studies made at the Memorial Hospital, in New York, stated that "patients who have had total gastrectomy for carcinoma of the stomach have an impaired ability either to digest or absorb the fat of the diet and, in one patient, the protein of the diet" In these same patients they observed "a refractory rather than a macrocytic anemia" MacDonald⁷ and associates, in 1947, reported studies on three patients who had survived total gastrectomy for three, five, and ten years, respectively The three and ten year survivors were said to be in excellent condition Their fat absorption was not significantly impaired The

TABLE I—*Total Gastrectomy*

Authors	Year of Report	Number Operations	Mortality
Finney and Reinhoff ⁸	1928*	67	55.8%
Pack and McNeer ⁹	1942*	298	37.6%
Vaugh and Fahland ¹⁶	1945	77	44.2%
Smith ¹⁰	1947	89	29.1%
Ransom ¹²	1947	60	23.0%
Pack, McNeer, Boohn ¹¹	1947	41	31.7%
Longmire ¹³	1947	20	10.0%
Smithwick ¹⁷	1947	10	20.0%

* Review of literature

TABLE II—*Gastrectomy Esophagojejunostomy*

Years	Number Operations	Number Deaths	Mortality
1938-1944	7	5	71%
1945-1948	11	2	18%
Total	18	7	39%

third patient, a five year survivor, who had a partial pancreatectomy in addition to total gastrectomy, showed impairment of fat absorption Two of the three patients developed a macrocytic hyperchromic anemia, two and five years after operation The third patient had prophylactic liver therapy and did not develop anemia

There is little information available concerning those patients who survive operation and later die from inanition Longmire¹³ reported two such patients among ten postoperative deaths Since both patients had been discharged from the hospital and apparently were receiving inadequate diets he concluded that these patients would have survived if they had been provided with ordinary dietary requirements In reporting 43 late deaths following total gastrectomy Smith¹⁰ stated that seven, or 16 per cent, died from inanition The details of these deaths are not recorded

Our observations lead us to believe that some deaths reported as due to metastases or a recurrence of the carcinoma actually may have been caused by inanition

CASE MATERIAL

Our experience in treating carcinoma of the stomach by gastrectomy with esophago-jejunostomy is limited to 18 cases. There were seven deaths, an operative mortality of 39 per cent. There have been only two fatalities among the 11 patients operated upon since 1944, an operative mortality of 18 per cent (Table II). The causes of death are shown in Table III. Three patients died from infection, presumably caused by a leak of the esophago-jejunal anastomosis, two died of shock, one developed a fatal pneumonia and one death was caused by a pulmonary embolus.

TABLE III—*Causes of Operative Deaths*

Name	Year	Survival Period	Cause of Death
A V	1940	3 Months	Peritonitis
T S	1940	1 Day	Shock
T E	1944	1 Day	Shock
H O	1944	6 Weeks	Peritonitis
K H	1944	15 Days	Pulmonary embolus
J F	1945	11 Days	Peritonitis
M N	1945	6 Days	Pneumonia

TABLE IV—*Causes of Late Deaths*

Name	Survival Period	Cause of Death
E H	4 Years	Metastases
F D	1 Year	Recurrence
B G	7 Months	Recurrence
P Q	10 Months	Recurrence
C G	6 Months	Recurrence
W B	7 Months	Inanition

Six of the 11 patients surviving operation are now dead. The survival period and the causes of death are shown in Table IV. One patient lived for four years before dying from metastases. The remaining five patients lived one year or less, four died because of a local recurrence of the carcinoma and one patient died from inanition although he had an excellent appetite and spent most of his postoperative life in the hospital where every effort was made to improve his nutritional state.

The present condition of the five patients who are alive is shown in Table V. Although it cannot be said that any of these people have been returned to a completely normal physical state, they are living fairly comfortable lives, one for 30 months, one for 22 months, two for three months and one for one month.

The present study is concerned primarily with the subsequent history of patients who have survived gastrectomy. We are reporting in some detail our observations on three patients. One lived for four years before dying from metastases, the second died from inanition seven months after operation and the third is alive and fairly well, 30 months after operation.

The first patient (E. H.) was operated upon in December, 1938, and the entire stomach was removed. She died in November 1942. Death was thought to be caused by metastatic carcinoma, this diagnosis being based on roentgen evidence of tumor in the pelvic bones, the presence of an enlarged liver and ascites. Post mortem examination was not done as the patient died in another hospital.

While this patient was never robust following operation and did not return to any gainful occupation, she led a reasonably comfortable life for more than

TABLE V—*Present Condition of Survivors*

Name	Postoperative Interval	Weight	Appetite	Food Capacity	Stools	Blood	Work
A. B.	30 Months	Loss 34 lbs	Poor	3 meals a day Occasional vomiting	Normal 1 per day No diarrhea	RBC 4.3 Hb 98% Serum protein 7.3	Light house work
M. L.	22 Months	Loss 10 lbs	Poor	Frequent feedings	2-3 per day Occasional diarrhea	RBC 4.0 Hb 80%	Regular Secretary
W. M.	3 Months	Loss 10 lbs	Good	Frequent feedings	Normal 1 or 2 per day No diarrhea	RBC 3.6 Hb 70%	None
J. R.	3 Months	Gain 10 lbs	Good	Frequent feedings	Normal, 2 per day No diarrhea	RBC 4.1 Hb 75%	None
A. W.	1 Month	Loss 2 lbs	Fair	Frequent feedings	Normal 1 or 2 per day No diarrhea	RBC 4.0 Hb 80%	None

three years before developing symptoms which presumably were due to metastases. Blood counts made at frequent intervals revealed an anemia, characterized by a hemoglobin of between 60 and 70 per cent and a red cell count of about 3,500,000, which persisted in spite of almost continuous iron (ferrous sulfate) and liver therapy. Coincident with the roentgen findings of bone metastases, three and a half years after operation, a marked increase in the degree of anemia was noted. It is the opinion of Dr. Luis A. Amill, who followed this patient in the hematology clinic, that at no time was the anemia of the primary type.

Although edentulous, this woman ate fairly well on her several admissions to the hospital, but due to her low economic status it is probable that her food intake at home was not ideal. Even so, she maintained a weight of between 90 and 100 pounds. Her normal weight had been about 110 pounds. She did not

at any time suffer from a disabling diarrhea and ordinarily had two or three bowel movements a day. Examination of the stool one year after operation showed a fat content of 49 per cent and at one year and nine months the fat content was 34 per cent.

A deficiency of protein digestion was suggested by persistently low total serum protein levels and the fact that it was repeatedly noted on the patient's chart that she had a mild nutritional edema.

The second patient (W B) was operated upon in July, 1947, and the entire stomach, except 3 cm of the pylorus was removed. He died of inanition in February, 1948. His course was uncomplicated until the eleventh postoperative day, when he developed diarrhea. This diarrhea persisted, with the exception of short periods of three or four days, until the patient's death seven months later. Intensive medical and dietary treatment failed appreciably to alter the number or character of the stools. The fat content of the stool determined on one occasion, six months after operation, was found to be 40 per cent.

This patient's normal weight was about 140 pounds although at the time of admission to the hospital he weighed only 120 pounds. Following operation his appetite was ravenous and after about two weeks he regularly consumed six feedings per day of a high protein, high caloric and high vitamin diet. His weight, on discharge from the hospital, five weeks after operation was 117 pounds.

He did not do well at home and was readmitted to the hospital, three weeks after discharge, complaining of a persistence of the diarrhea and a weight loss of 19 pounds. This patient spent the remainder of his life, about five months, in the hospital where strenuous efforts in the way of oral and parenteral feedings were made to improve his nutritional status.

In spite of the high protein diet, supplemented by oral and intravenous protein hydrolysates, serum protein values dropped from an immediate postoperative level of 7.4 Gm per cent to less than 6 Gm per cent, and remained below this level. A mild though progressive dependent edema was present. During the last month of life the edema was quite marked and ascites developed.

A mild degree of anemia, as indicated by an average hemoglobin value of 75 per cent and a red cell count of about 4,000,000 persisted in spite of ferrous sulfate therapy. Liver was not given to this patient.

Post mortem examination showed extreme emaciation. There was practically no subcutaneous fat and the omentum as well as the mesentery of the intestines was devoid of fat. There was no evidence of carcinoma, local or metastatic. Consolidation of the right lower lobe of the lung was present but this was regarded as a terminal development. The primary cause of death appeared to be starvation, due to an inability to digest or absorb adequate food from the intestinal tract.

We had no satisfactory explanation as to why this patient was unable to digest enough food to sustain life. One possible factor is that in 1937, 10 years before the gastrectomy, the patient's right colon had been removed because of a carcinoma of the hepatic flexure. However, excellent health for

nine years following the partial colectomy suggests that this operation had little to do with his failure to maintain a satisfactory nutritional state following gastrectomy

The third patient (A B), a 59-year-old woman, was operated upon in October, 1945, and the entire stomach, except approximately 4 cm of the pylorus, was removed. In April, 1948, 30 months later, she was in fairly good health, able to do her own shopping, and a large part of her usual housework. The most striking feature of this patient's course has been a total weight loss of 34 pounds, 6 pounds of it in the past year. She has not had a particularly good appetite, but does eat three small meals a day and further supplements her food intake by candy between meals. The chronic constipation complained of prior to operation disappeared and the patient has had one large but normal bowel movement each day. Medication has been limited to an iron compound and multiple vitamin tablets. At the last examination, 30 months after operation, the blood count was 4,300,000 red blood cells with a hemoglobin of 98 per cent and the total serum protein was 7.3 per cent.

COMMENT

As previously indicated, two cases included in this report are not true total gastrectomies. In one (W B) 3 cm of the pylorus was not removed and in the second (A B) approximately 4 cm of the pylorus was left. The small amount of gastric mucosa was spared in the hope that its presence might reduce the nutritional difficulties which are known to occur in some patients subjected to total gastrectomy.

The preservation of gastric mucosa in the patient (W B) had no apparent beneficial influence on his most unsatisfactory course. The outcome in the second patient (A B) with approximately 4 cm of pylorus, has been satisfactory except for a marked weight loss.

Our experience with two other patients, not included in this series, strengthens the impression that even small amounts of gastric mucosa may be of benefit to the patient. The first of these patients (H M) had an almost complete gastrectomy for the removal of a neurofibroma of the fundus, only 6 cm of the cardia being left. This man, after a long convalescence during which the "dumping syndrome" made his life most uncomfortable, returned to work as an automobile mechanic. On the last examination, 22 months after operation, he was gaining weight and weighed 132 pounds. Normal preoperative weight was 156 pounds. He had a fairly good appetite and regularly ate six small meals a day. Bowel movements were normal and there was no anemia.

The second patient (J U) was operated upon for the removal of a gastric carcinoma. All the stomach, except 6 cm of normal appearing pylorus, was excised and the esophagus was anastomosed to the remnant of pylorus. Convalescence was prolonged due to stricture at the site of anastomosis but at the last examination, 12 months after operation, this man appeared to be in good health. He had a fairly good appetite although a limited food capacity forced him to eat frequent small meals. His weight was 105 pounds, a gain of about

nine pounds since discharge from the hospital. Preoperative weight had been 116 pounds. Examination of the blood revealed a hemoglobin of 94 per cent, 4,700,000 red blood cells and a total serum protein of 7.4 Gm per cent.

No definite conclusions can be drawn from the small number of cases herein reviewed, but three of the four patients in whom a small amount of stomach was retained appear to have enjoyed a better nutritional state than those in whom the entire stomach was removed. This observation is in accord with that of Finney and Rienhoff⁸ and suggests that further observations are needed on this and other points connected with total gastrectomy. It is disturbing to have a patient survive total gastrectomy only to die later of inanition after apparently being cured of his carcinoma.

SUMMARY

1 Eighteen patients with carcinoma of the stomach were treated by total gastrectomy. There were seven deaths, an operative mortality of 39 per cent.

2 Six of the 11 survivors are now dead. One patient lived for four years, one for one year and four died within one year following operation.

3 Five of the six deaths were due to a recurrence of the carcinoma. One patient died of inanition seven months after operation although his food intake had been adequate. Post mortem examination revealed no evidence of carcinoma.

4 Five patients were alive at the time of this report. One for 30 months, one for 22 months, two for three months and one for one month.

5 The four patients followed from one to four years have maintained a fairly satisfactory, though subnormal nutritional state.

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CHEMOSURGICAL TREATMENT OF TUMORS OF THE PAROTID GLAND^{*†}

A MICROSCOPICALLY CONTROLLED METHOD OF EXCISION

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IN THE TREATMENT OF TUMORS of the parotid gland the main object is the complete removal of the neoplasm. A second object is the preservation of as much as possible of the facial nerve which traverses the parotid gland. The attainment of these goals is facilitated by the use of the chemosurgical technic which, by virtue of its microscopic control of excision, enables the eradication of neoplasms with an unusually high degree of reliability and with maximal conservatism. The development of the chemosurgical method in the laboratory¹ and in the clinic,² and its application in the treatment of cancer of the lip,³ nose,⁴ ear,⁵ eyelid,⁶ face,⁷ extremities and trunk⁸ and skin⁹ have been described

TECHNIC

The chemosurgical technic as applied to the excision of tumors of the parotid gland will be described in the case report which follows

Case Report—W H, male, age 80, was admitted to the Wisconsin General Hospital complaining of a growth under the left ear. The lesion which began as a deep-seated mass in the parotid gland was first noticed by the patient about 6 months previously. The mass had grown rapidly despite radium and roentgen ray therapy. One month before admission a lobule in the posterior portion of the mass had rapidly broken through to the surface of the skin and an ulcer had developed at its apex.

Just below the ear and impinging upon it was a deep-seated mass which measured 6.5 by 8.0 cm (Fig 1A). Near the posterior edge there was a protrusion which measured 3.5 by 4.5 cm, and in the center of this was an ulcer which measured 1.7 by 1.9 cm. The mass pressed up against the ear and external auditory canal with resulting deformity of these structures. The neoplasm was firmly fixed to the parotid gland and other deeper structures. There was no facial paralysis.

Following premedication with 0.015 Gm of morphine sulfate the first step in the treatment of this lesion was the application of a keratolytic, dichloroacetic acid, to the portion of the mass covered by skin. Whitening of the skin served to indicate when the keratin layer had been penetrated and rendered permeable to the zinc chloride. The zinc chloride fixative paste was then applied in a thickness of about 3 mm. The paste contained stibnite (80 mesh sieve), 40 Gm, powdered sanguinaria, 10 Gm, and saturated solution of zinc chloride, 34.5 cc. The treated area was covered with a thin layer of cotton and then by a layer of cotton on which petrolatum had been spread to make a moisture-tight closure.

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After 24 hours a layer of tissue about 1 cm thick was excised. There was no pain or bleeding from this operation because the incision was made through killed and fixed tissue. The presence of neoplasm was evident upon gross inspection. Frozen sections of the fixed tissue revealed the presence of a squamous cell carcinoma with a degree of malignancy of grade 3 (Fig 4A). The fixative was reapplied.

During the next four days the tumor mass was removed in successive layers without microscopic examination of the excised tissues. On the fifth day, however, it became impossible to differentiate grossly between normal and cancerous tissues in some areas



FIG 1—(A) Parotid carcinoma which had grown rapidly over a period of six months and had failed to respond to x-ray and radium treatment. The main mass was deep-seated but there was an ulcerated protrusion of one month's duration from the posterior part of the neoplasm. (B) Lesion after separation of the final layer of fixed tissue except for a portion over the sternocleidomastoid muscle near the lower edge. Deep extensions from the main mass which followed along the perimesium of the stylohyoid muscle and along the perineural lymphatics of the auriculotemporal nerve were removed by multiple microscopically controlled excisions. (C) Healed lesion two months later. There was no facial paralysis except for the muscles of the chin supplied by the mandibular branch. The patient was free of cancer after seven years.

Therefore, the layers of tissue from the areas in question were divided into specimens of convenient size, frozen sections were cut through the under surface of each by means of microtechnical procedures which have been described.¹⁰ The sections were scanned under the microscope and the areas of cancer so found were marked with red pencil on a map drawn on a pad of paper. This map corresponded to a map drawn on the lesion with merbromin during the excision of the specimens. Reapplication of the fixative was then limited to the areas demonstrated to be cancerous by microscopic visualization.

This process was repeated daily until the 20th day when the removal of the last extension of the cancer was completed. In some areas the microscopically visualized extensions of the neoplasm extended more than 2 cm beyond the grossly visible portion. One extension followed the perineural lymphatics of the auriculo-temporal nerve for several millimeters while another followed the perimesium of the stylohyoid muscle. Without the systematic microscopic control afforded by the chemosurgical method these extensions undoubtedly would have been missed.

TUMORS OF THE PAROTID GLAND

It is important to emphasize that the technic made it feasible to examine every square millimeter of the lesion under the microscope and to proceed till the entire area was free of cancer

Five days after reaching a cancer-free plane the thin final layer of fixed tissue had become demarcated so that most of it could be dissected off (Fig 1B) Upon return for checkup two months later the lesion had completely healed with a fine linear scar (Fig 1C) The patient was free of cancer when last seen seven years later Despite the extensiveness of the lesion there was no facial nerve paralysis except for the unimportant mandibular branch

In the absence of palpable regional nodes and in consideration of the advanced age of the patient a neck dissection was not done In a younger patient with a carcinoma of such large size and high malignancy, a prophylactic

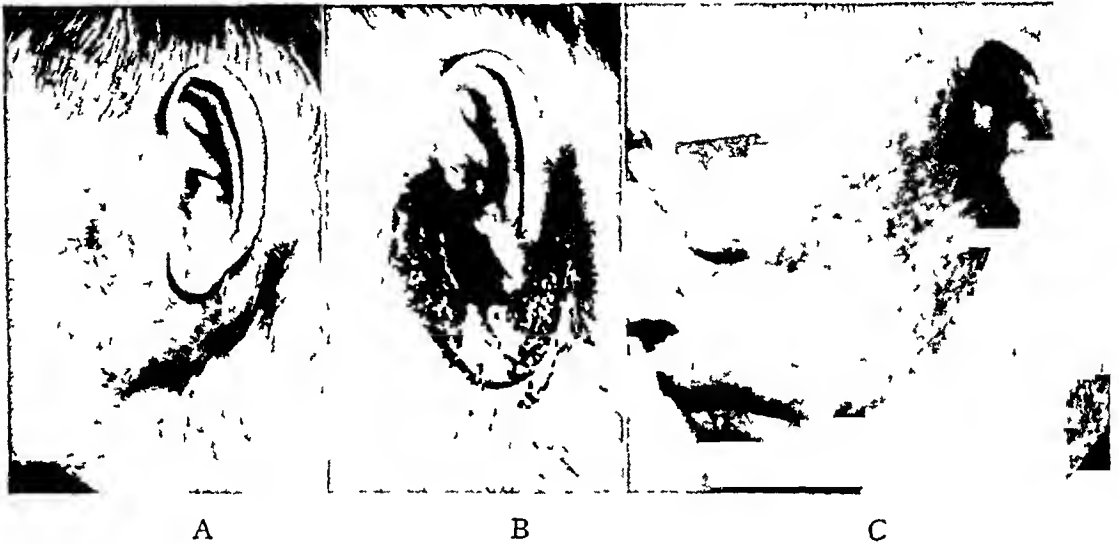


FIG 2—(A) Carcinoma of the parotid gland One year prior to admission, a mass which had been diagnosed "mixed tumor of the parotid" was surgically excised and the area treated with x-ray The recurrent mass was hard and fixed and it measured 60 by 63 mm (B) Lesion after chemosurgical excision Because of the definitely infiltrative character of the neoplasm (Fig 4B) a diagnosis of carcinoma was made The neoplasm infiltrated around the main branches of the facial nerve so complete paralysis resulted from the chemosurgical removal The inferior wall of the external auditory canal was also invaded (C) Healed lesion three months later The complete facial paralysis is apparent There has been no recurrence after three years

neck dissection would have been recommended Palpable enlargement of the nodes also would have called for neck dissection It may be advisable in some cases to do both a carotid ligation and a lymphadenectomy during or prior to chemosurgical excision of the primary lesion Such a procedure not only would accomplish the removal of the nodes suspected of containing cancer but it would also avoid the danger of hemorrhage during the chemosurgical treatment of the parotid lesion

In some cases in which deep invasion into the region of the external carotid artery is foreseen the ligation of this vessel just above the carotid bifurcation is advisable in order to prevent hemorrhage during separation of the final layer of fixed tissue There were four instances of bleeding sufficient to require

a suture-ligature or a pressure dressing in the 17 cases in this series. This complication could have been avoided by ligation of the external carotid, either before institution of chemosurgical treatment or after the sections had revealed that there were deep extensions of cancer along this vessel. No instance of serious hemorrhage occurred in the patients whose cases are reported in this series.

In two patients whose cases are reported in this series the external carotid artery was ligated. One ligation was done prior to the institution of chemosurgical treatment because the carcinoma obviously had extended very deeply. The other ligation was carried out because it was determined, during chemosurgical treatment, that the carcinoma had extended around this vessel.



A

B

C

Fig 3—(A) Carcinoma of the parotid of two years' duration. A tumor had been excised in another department and the area treated with radium one year before he was admitted to the chemosurgical department. (B) Lesion after chemosurgical excision in nine microscopically controlled stages and after separation of the final layer of fixed tissue. The carcinoma (Fig 4C) extended onto the bone of the external auditory canal, the temporal bone, the zygoma and the condyloid process of the mandible which structures are shown in the base of the wound. Some areas of mixed tumor were found indicating that the carcinoma arose in a pre-existing mixed tumor. The carcinoma invaded for several millimeters along the perineural lymphatics of the branch of the facial nerve (Fig 4D) to the frontalis muscle which was paralyzed. (C) Healed lesion with partial closure of the auditory canal. The lack of lower facial paralysis is evident. There was some weakness of the lower eyelid so that a tarsorrhaphy was done although this probably was unnecessary. The patient is free of cancer after four years.

Some neoplasms of the parotid gland retain considerable secretory function and the lesion may be so moist that penetration of the fixative chemical is reduced due to dilution. In several cases it was necessary to reapply the fixative twice instead of once daily.

Salivary fistulas which persisted for periods of from one week to 21 months were encountered in 15 of the 17 patients whose cases are reported in this series. In only four cases did the fistula persist longer than three months. During the healing of lesions of the parotid gland after chemosurgical treatment, part of the surface is covered by epithelium derived from the parotid ducts. Ordinarily, this parotid epithelium is gradually replaced by the

epithelium of the skin, the latter apparently being more able to survive the conditions on the surface of the body. However, if complete replacement by the skin epithelium does not occur promptly, the fistula may be eradicated by the simple expedient of applying the zinc chloride fixative to the exposed

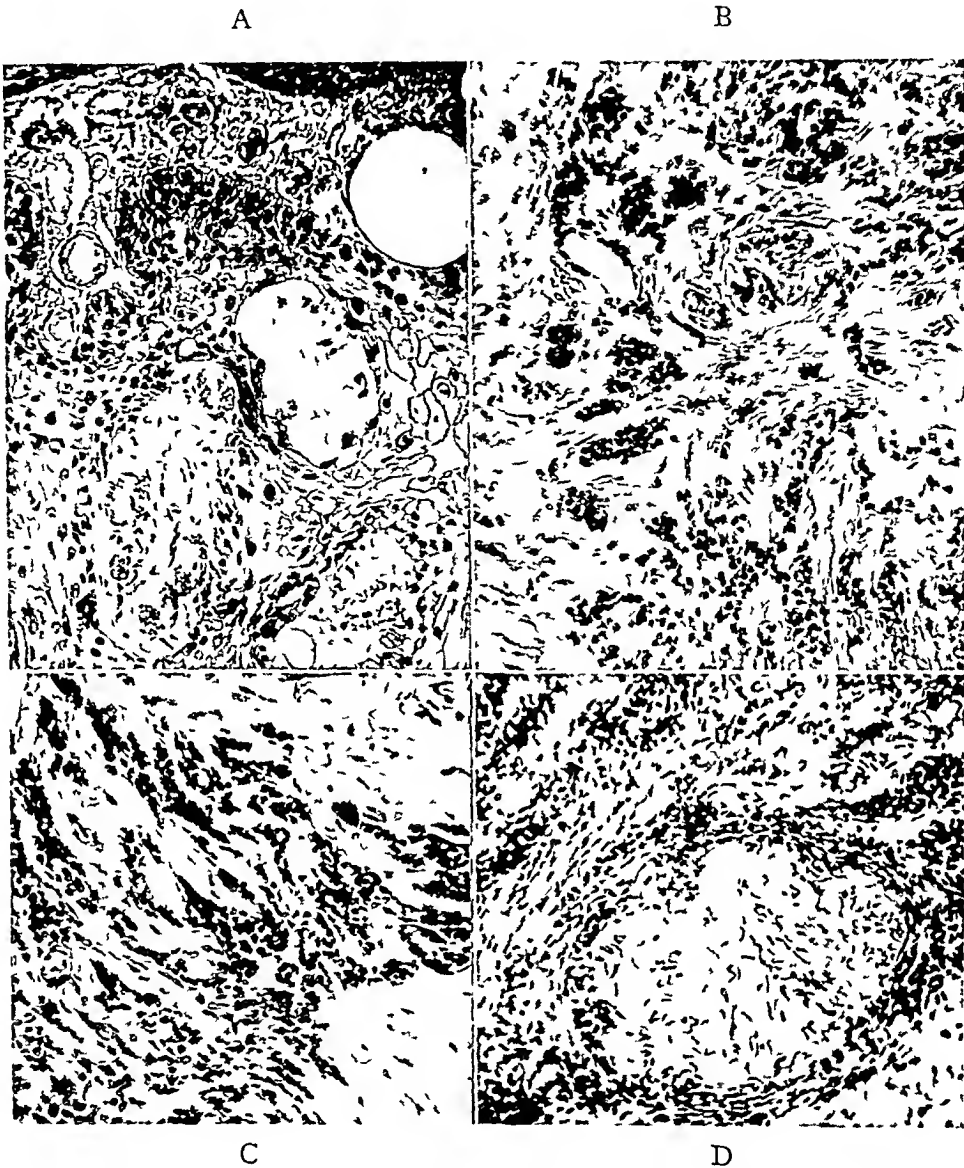


FIG 4—Sections of parotid carcinomas after fixation *in situ* by zinc chloride (A) Squamous cell carcinoma from patient shown in Fig 1. The large clear cells were degenerated rather than keratinized. The degree of malignancy was considered grade 3. (B) Carcinoma from patient shown in Fig 2. A moderate degree of invasiveness is evident. (C) Carcinoma from patient shown in Fig 3. This moderately invasive neoplasm arose in a pre-existing mixed tumor. (D) Same tumor, showing perineural invasion.

parotid epithelium. In every case in this series in which troublesome parotid fistulas were encountered, this method was effective in eliminating the condition. Even an apparently permanent fistula of 21 months' duration was healed in ten days after institution of this treatment.

THERAPEUTIC RESULTS IN CASES OF CARCINOMA OF THE PAROTID GLAND

Thirteen carcinomas of the parotid gland were chemosurgically treated during the seven-year period ending November 30, 1944, which date is over three years prior to this writing. Most of the lesions were large and deep-seated. Nearly two-thirds of the patients (63.6 per cent) had received previous unsuccessful surgical excision or radiation treatment. In none of the cases was the presence of metastasis recognized at the onset of treatment.

End Results After Three Years or More—The 13 cases observed for three years or more were divided into "indeterminate" and "determinate" groups according to the plan of Martin, MacComb and Blady.¹¹ The indeterminate

TABLE I—*End Results of Chemosurgical Removal of Carcinoma of the Parotid Gland*

This series includes the cases of all patients with histologically proven carcinomas both early and advanced, previously untreated and recurrent who were admitted to the chemosurgery clinic from March 26, 1938 to November 30, 1944 for the three year group and from March 26, 1938 to May 1, 1943 for the five year group.

	Three Year Period	Five-Year Period
Total number of cases	13	12
Indeterminate group		
Patients without recurrence dead from other causes	1	1
Patients without recurrence lost from observation	1	1
Total number	2	2
Determinate group		
Total number	11	10
Unsuccessful results		
Patients dead as a result of cancer	4	4
Patients with cancer lost from observation	0	0
Patients with cancer living	0	0
Total number	4	4
Successful results		
Patients free from cancer for three years or more	7	
Patients free from cancer for five years or more		6
Three year end results		
Total number of cases with successful results divided by total number of determinate cases (7-11)	63.6%	
Five-year end results		
Total number of cases with successful results divided by total number of determinate cases (6-10)		60%

group included one patient who died of other causes before the expiration of three years without recurrence of the cancer and one patient who was lost from observation without evidence of cancer when last seen. The determinate group included the unsuccessful results of which there were 4 and the successful results of which there were 7. Thus, in the three-year period successful results were obtained in 63.6 per cent of the 11 cases in the determinate group (Table I).

End Results After Five Years or More—In the group of 12 cases observed for five years or more, there were two cases in the indeterminate group and ten cases in the determinate group. In the five-year period, successful results were obtained in 60 per cent of the ten cases of the determinate group (Table

I) In one case which was illustrated in a previous article² the patient has remained free of cancer for eleven years

Effect of Size of Lesion on Prognosis—As was to be expected the rate of cure was greater for the smaller lesions than for the large (Table II). Thus, while 100 per cent of the lesions under 4 cm in diameter were cured, only 50 per cent of the lesions over 4 cm in diameter were cured. However, it is not the lesion's extensiveness *per se* that reduces the curability of parotid carcinomas, but it is the increased chance of metastasis or involvement of vital structures that impairs the prognosis of patients with lesions of large size. Thus, in this series in which there were four unsuccessfully treated patients there were two failures due to the development of metastases, one failure due to extremely extensive permeation along the perineural lymphatics and one operative death resulting from pulmonary edema and bronchopneumonia in a patient who was in very poor condition when therapy of the extremely advanced parotid tumor was instituted. Therefore if there has been no complication such as metastasis or involvement of vital structures, it is possible chemosurgically to excise even the most extensive tumor.

TABLE II—*Effect of Size of Carcinoma of Parotid Gland on Prognosis*

Group	Average Diameter (cm)	Number of Lesions	Successful Results	
			Number	Per Cent
A	Under 2	0		
B	2 to 4	3	3	100
C	4 to 6	4	2	50
D	6 or more	4	2	50
All groups		11	7	63.6

Effect of Previous Treatment on Prognosis In the group of eleven cases of carcinoma of the parotid gland in the determinate group, seven lesions (63.6 per cent) had recurred after previous unsuccessful surgical excision or radiation therapy. Although it would be expected that previous treatment would have an unfavorable influence upon prognosis, the opposite seemed to be true in this series of cases. Thus, in the seven cases in which the patient had recurrent carcinoma, the neoplasm was successfully treated with the chemosurgical technic in five (71.4 per cent) while in the four cases of patients with lesions which had not received previous treatment, successful results were obtained in only two (50 per cent). While too much significance should not be attached to the statistics in this small series of cases, it is evident that the chemosurgical method is particularly useful in the treatment of recurrent lesions because these would otherwise carry a very poor prognosis. The only adverse influence previous unsuccessful treatment has upon the prognosis as far as chemosurgical treatment is concerned is occasioned by the delay which allows metastasis and invasion of vital structures to occur.

Effect of Histologic Grade of Malignancy on Prognosis—Although there is no generally accepted classification of carcinoma of the parotid gland into

well defined grades of malignancy, a definite impression was gained that prognosis is strongly affected by the histologic degree of malignancy. Thus, in a group which we have classified as "moderately invasive carcinoma" (*e g*, Fig 4B) all four cases were successfully treated while in another group of four cases placed under the classification "highly invasive carcinoma" the rate of cure in the three-year period was only 50 per cent. The latter group includes the one squamous cell carcinoma in this series (Fig 4A). The remaining three cases were placed under the classification "moderately invasive carcinoma arising from a mixed tumor" (*e g*, Fig 4C & D) and in this group the rate of cure was 33.3 per cent. The unsuccessful treatment of two cases in this group is readily accounted for on the basis of the extremely extensive nature of the neoplasms rather than on their degree of malignancy. The two unsuccessfully



FIG 5—(A) Benign mixed tumor of the parotid gland of eight years' duration (B) Healed lesion. The lack of paralysis is evident. There has been no recurrence of the tumor after nine years.

treated cases in the group of highly invasive carcinomas had unfortunate outcomes because of metastasis in one and because of widespread invasion of the perineural lymphatics in the other. The successfully treated case in this group was a deep-seated carcinoma with cervical metastasis, the patient was well five years after chemosurgical removal of the primary lesion followed by surgical dissection of the cervical nodes.

Effect of Site of Origin on Prognosis—The site of origin of the carcinoma had relatively little effect on the prognosis. Thus in the eight cases arising in the retromandibular area, five were successfully treated (62.5 per cent) while in the group of three cases which arose in the preauricular region, successful results were attained in two (66.6 per cent).

Effect of Metastasis on Prognosis—Since no metastatic nodes were noticed on the first visit in any of the patients in this series no definite data is available

regarding the effect of initially diagnosed metastasis on prognosis. In three cases metastases were noticed some time after the initial treatment of the primary carcinoma. In one case an upper cervical mass was noticed three months after treatment of the primary lesion, but the patient refused lymphadenectomy and went to a faith healer. When she returned in six months the mass was inoperable, so 10 roentgen ray treatments were given for palliation. In a second case the cervical metastasis was noticed six months after removal of the primary lesion, but a neck dissection was not recommended because of advanced age and poor general condition, palliative roentgen ray therapy was given. In a third case, metastasis had developed when the patient returned for belated checkup after eighteen months. Though the original carcinoma was in the preauricular region a new mass had appeared in the postauricular region.



FIG 6—(A) Benign mixed tumor of the parotid gland of 28 years' duration. It had been excised twice and the patient had received one course of six roentgen treatments. (B) Lesion after chemosurgical excision which required twenty-four days. The final layer of fixed tissue had separated except for one area under the ear where a rather deep, unpredicted extension of the neoplasm had been followed out. The protruding tissue in the lower part of the wound is normal submaxillary salivary gland tissue. (C) Healed lesion showing absence of facial paralysis except for the unimportant mandibular branch. There has been no evidence of recurrence after more than three years.

The latter was chemosurgically excised and the cervical nodes were excised by a member of the surgical staff. There was no evidence of recurrence after five years.

THERAPEUTIC RESULTS IN MIXED TUMOR OF THE PAROTID GLAND

Inasmuch as surgical excision of benign mixed tumors of the parotid gland is a fairly reliable procedure, most of the patients who entered this hospital with this condition were treated surgically rather than chemosurgically. For that reason this series includes the cases of only four patients who were chemosurgically treated. Successful results were attained in all four of these cases in the three-year period. In the five-year period there were two cases, and in both successful results were obtained. None of the patients had been previously treated. Two of the tumors were of large size (Figs 5 and 6) while two were somewhat smaller with average diameters of 57 mm and of 30 mm. Facial

nerve paralysis developed as a result of chemosurgical treatment in only one of the four patients (Fig 6) and in this case it was the unimportant mandibular branch which was interrupted

DISCUSSION

The chief advantage of the chemosurgical treatment of carcinoma of the parotid gland is the increased reliability which is attained by virtue of the systematic microscopic control of excision. The therapeutic results compare very favorably with those attained in other clinics by the use of ordinary surgical, electrosurgical and radiation technics (Table III). There is probably some degree of discrepancy in the comparison of the results reported from the various clinics because of differences in histologic interpretation. Thus, some workers consider almost all parotid tumors to be at least potentially

TABLE III—*Comparison of the End Results of Chemosurgical Treatment of Carcinoma of the Parotid Gland with the End-Results of Other Treatments after Observation for Three Years or More*

Author	Treatment	Number of Determinate Cases	Successful Results	
			Number	Per Cent
Mohs	Chemosurgery	11	7	63.6
Ahlbom ¹²	Surgery plus radium	81*	27	33.3
Swinton and Warren ¹³	Surgery	6	2	33.3
Quattlebaum, Dockerty and Mayo ¹⁴	Surgery (plus roentgen therapy in some)	19†	6	31.6
Martin ¹⁵	Surgery (plus radium in some)	13	2	15.4
Stein and Geschickter ¹⁶	Surgery	21	3	14.3
Benedict and Meigs ¹⁷	Surgery	30	1	3.3
Wakeley ¹⁸	Surgery	12	0	0
Janes ¹⁹	Surgery	2	0	0
Martin ¹⁵	Radiation	6	0	0

* Both the malignant and semimalignant neoplasms are included

† Adenocarcinomas of cylindroma type only

malignant, and therefore classify them all as carcinoma. Others consider only the highly anaplastic and actively invasive neoplasms to be carcinoma and classify the rest as mixed tumors. Some, Ahlbom¹² for example, take a middle stand and maintain that there are numerous borderline types which are not clearly benign or clearly malignant and which may be classified as semi-malignant. I find the last position is most consistent with my experience, and I feel that these "semi-malignant" tumors may justifiably be placed in the malignant group. Therefore, in the present series the neoplasms are considered malignant if they have definite infiltrative characteristics. While most of the cases fell quite distinctly into either the benign or malignant group, there were three carcinomas derived from mixed tumors, which might be classified as semi-malignant (*e g*, Fig 4C & D). Since in two of these possibly doubtful cases unsuccessful results were obtained, there would be an increase in the rate of cure rather than a decrease if these cases were omitted from the series of malignant lesions.

Next to reliability the advantage of conservatism is most important. Since only 1 or 2 mm beyond the level of neoplastic extension at any given point need be destroyed by the chemosurgical technic, it is possible to preserve a maximum amount of normal tissue. This is particularly important in regard to the facial nerve. In the present series of rather extensive carcinomas of the parotid gland, it seems likely that radical surgical extirpation would have produced complete facial paralysis in every case. By the use of the chemosurgical technic, however, it was possible to preserve the entire nerve in one case and to preserve part of the nerve in four others. In three cases there was

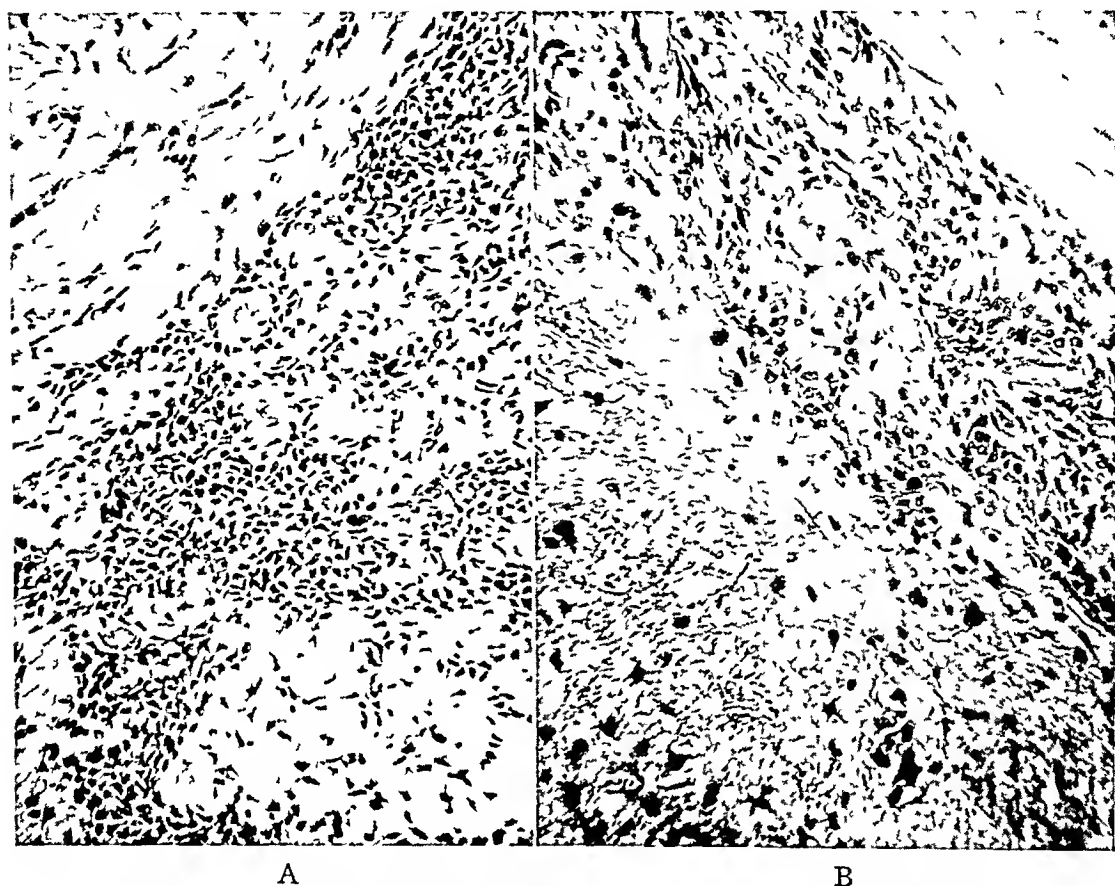


FIG 7—Sections of mixed tumors of the parotid gland after fixation *in situ* by zinc chloride. (A) Tumor from patient shown in Fig 5. (B) Tumor from patient shown in Fig 6.

initial paralysis from previous treatment or from carcinomatous invasion. Less paralysis was encountered in the treatment of neoplasms in the lower retro-mandibular region than in the treatment of lesions in the preauricular region. However, one preauricular carcinoma was chemosurgically excised with paralysis of only the branches to the eyelid and forehead (Fig 3). In three cases there was some return of nerve function after paralysis for periods of from one week to two years.

Both the reliability and conservatism exhibited by the chemosurgical treatment of carcinoma of the parotid gland are the results of the microscopic control which the technic provides. This microscopic control is needed because

most carcinomas of the parotid gland tend to send out grossly invisible extensions into the surrounding tissues. Thus, in this series, there were three neoplasms which had a strong tendency to follow the perineural lymphatics, in one case, the cancer cells extended in these structures for fully 5 cm beyond the confines of the main tumor mass. In several cases the carcinoma followed for some distance along the perichondrium of the cartilages of the external auditory canal. In none of the cases of this series was the carcinoma limited to the parotid gland itself. Many of the extensions were so slender or the cancer cells were so intimately interspersed between the normal cells, that it was impossible to locate and remove them with any degree of accuracy without the microscopic control afforded by the chemosurgical method. I believe that the unpredictability of these outgrowths is the chief cause of the poor results obtained with radical surgical extirpation of the parotid gland. In retrospect it is clear that in every case of carcinoma in this series, the neoplasm extended in such a way that removal of the parotid gland alone would not have resulted in a cure.

Besides the advantages of reliability and conservatism, the low operative mortality is also an advantageous feature of the chemosurgical method. Thus, in this series there was only one death during the course of treatment. In that case the presence of an extremely extensive neoplasm in a patient who was in very poor general physical condition constituted a situation that led to fatal pulmonary edema and bronchopneumonia.

The chemosurgical technic is not without some disadvantages. The multiple stages required for the chemosurgical excision of an advanced neoplasm of the parotid are somewhat time-consuming for the operator and painful for the patient. However, since these advanced neoplasms probably would be fatal otherwise, these disadvantages seem relatively insignificant. Another disadvantage is that special training and constant practice with the technic are essential for the best results and a special clinic with provisions for the preparation of frozen sections of an unusual kind¹⁰ is required.

SUMMARY AND CONCLUSIONS

The chemosurgical technic as used in the excision of tumors of the parotid gland is described and the therapeutic results in a series of thirteen carcinomas and four benign mixed tumors of the parotid gland are analyzed. The rates of cure in the series of patients with carcinoma of the parotid gland were 63.6 per cent in the three-year period and 60 per cent in the five-year period of observation.

All of the patients with benign mixed tumor of the parotid gland were successfully treated, there were four in the three-year period and two in the five-year period of observation.

The unprecedented reliability and conservatism of the chemosurgical method of excision are the results of the microscopic control which makes it possible to accurately follow out the "silent" outgrowths from the main tumor mass.

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RESECTION OF THE STERNUM FOR METASTATIC CARCINOMA*

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RESECTIONS OF VARIOUS PORTIONS of the sternum have been reported upon several occasions ^{1, 2} The effects upon the cardiorespiratory systems that accompany instability of this large and important portion of the thoracic wall has limited the indications for its removal to malignant diseases affecting it In previously reported cases, malignant diseases of the sternum requiring resection have generally been tumors arising primarily within it ^{1, 2, 3} Few metastatic lesions in the sternum have been surgically removed ² Macey and Phalen,⁴ in reporting two lesions of the sternum secondary to primary pulmonary adenocarcinomas, suggest that an attempt should be made to remove such lesions if they have not extended too widely The usual contraindication is the presence of other osseous or pulmonary metastases

It is the purpose of this report to describe the successful removal of a malignant tumor of the sternum metastatic from a previously removed carcinoma of the breast, and the use of a large tantalum plate to restore immobility of this portion of the thoracic wall

Case Report—E O, a 58-year-old white female, was admitted July 6, 1945, with a nodule in her right breast of several weeks' duration Her history and physical examination was not unusual Roentgenograms of her chest and spine showed no metastases She was subjected to a right radical mastectomy on July 10, 1945 Subsequent split-thickness skin grafts were required to close the defect over her anterior thoracic wall Histologic examination of the lesion showed a scirrhous and medullary adenocarcinoma infiltrating mammary fat No lymph node metastases could be demonstrated

Examination on January 13, 1948, revealed a 3 x 2 x 1 cm hard, fixed tumor situated in the midline over the upper portion of the sternum Roentgenograms of her chest and spine showed no metastases A biopsy of the tumor showed adenocarcinoma of the same cell type as in the original lesion Laboratory examinations demonstrated a mild anemia

Operation On January 31, 1948, under endotracheal nitrous oxide, oxygen, ether anesthesia, an incision was made over the medial one-half of each clavicle and inferiorly down to the xiphoid process, encompassing the tumor, which was located over the manubrium (Fig 1 inset) Skin flaps were reflected upon either side exposing all the costal cartilages down nearly to the xiphoid process Following a subperiosteal dissection of the clavicle upon either side, and using a Gigli saw, both clavicles were divided at the junction of the middle and proximal one-third The first, second, and third ribs upon the right were then exposed subperiosteally and divided at the costochondral junction The internal mammary vessels upon the right were ligated and divided in the first interspace The loose fat and areolar tissue of the anterior mediastinum was then carefully dissected from the under surface of the sternum which was divided obliquely, through its body, from the third interspace upon the right to the second interspace upon the left Both pleural cavities were opened and respiration was carried on with intermittent positive pressure Following division of the first and second ribs upon the left, the lesion was removed

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RESECTION OF STERNUM IN CARCINOMA

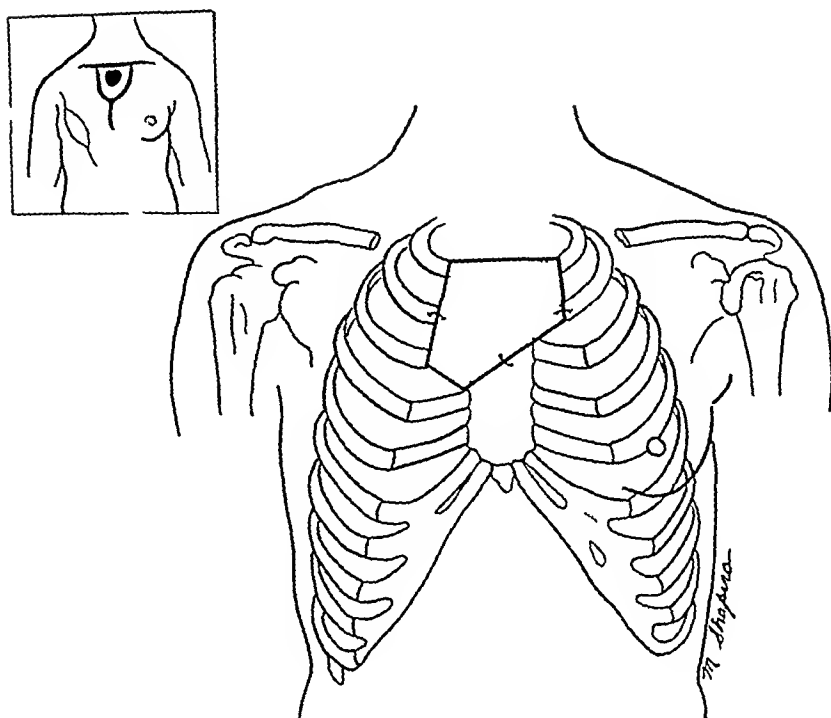


FIG 1—Diagram showing amount and location of the resected portion of the sternum and tantalum plate fixed in position

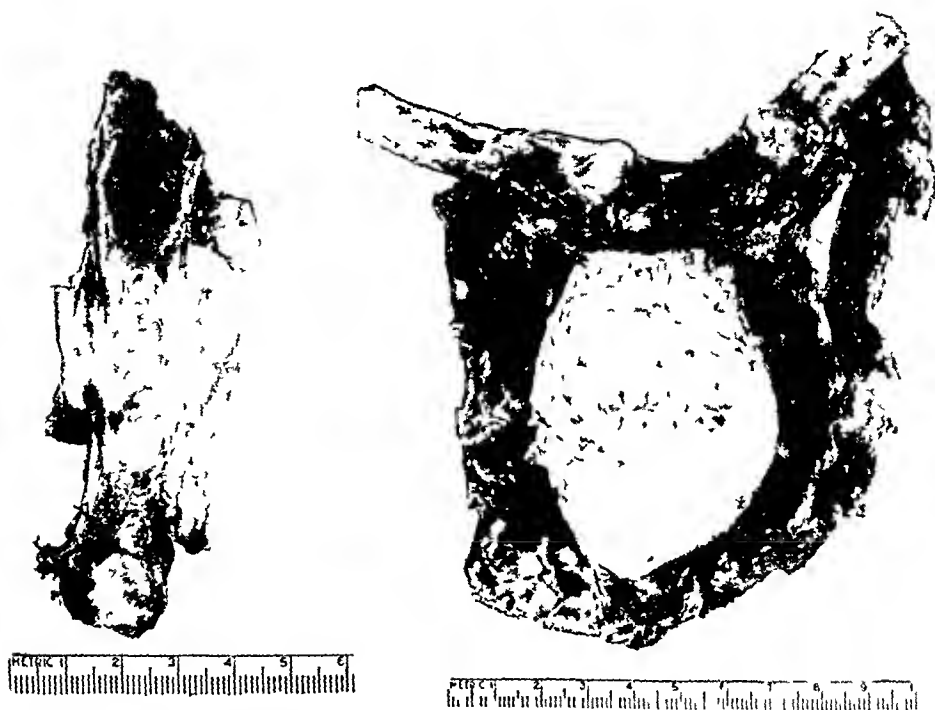


FIG 2—Longitudinal and frontal views of removed specimen after fixation in formalin. In the longitudinal view the lesion can be seen to extend completely through the sternum.

together with the proximal one-third of each clavicle, all of the manubrium, and approximately one-half of the body of the sternum (Figs 1 and 2) The internal mammary vessels upon the left were divided and ligated The rent in the pleura on the left side was easily closed with interrupted fine cotton sutures The pleural defect upon the right, however, could not be closed in this manner Accordingly, a large square of fascia lata was obtained from the right thigh, and sutured securely over the entire exposed anterior superior mediastinum, thus closing the right pleural defect An intercostal catheter was



FIG 3—Roentgenogram made fourteen weeks following operation showing tantalum plate in position

left in place in the fourth interspace upon the right A large tantalum plate, 12.2 cm wide, 14.0 cm long, and 0.0375 cm (0.015 inch) thick was fashioned to fit the bony defect Each upper corner of the plate was mortised into the end of the first rib upon either side Similarly, it was wedged into the second rib, but in addition was wired into place, using fine tantalum wire A third wire fixed the bottom of the plate into the obliquely cut body of the sternum (Fig 1) The plate, thus, seemed quite secure The sternocleidomastoid and the sternal attachments of the ribbon muscles of the neck were sutured to the upper aspect of the pectoralis major upon the left, and to the subcutaneous tissue upon the right Because of the defect in the skin, occasioned by excision of the skin overlying the tumor, it was necessary to rotate a flap of skin and subcutaneous tissue from the left side The skin and subcutaneous tissue was closed in two layers with fine No 60 cotton. Penrose

RESECTION OF STERNUM IN CARCINOMA

drains were left under the skin for 48 hours. The patient received 1500 cc of whole blood during the procedure.

Postoperative Course Her convalescence was quite uneventful. Small hematomata were aspirated from beneath the skin occasionally for three weeks, following which the wound appeared to be well healed with no evidence of an accumulation of serum or blood beneath the skin or plate. Forcible respiration does not buckle the plate. At the date of this writing, the plate remains securely in place eight months after operation, and causes no discomfort to the patient. There is no evidence of other local or distant metastases.

Comment The surgical removal of metastatic carcinoma anywhere in the body must be considered a palliative procedure. Occasionally, however, such lesions appear to be unaccompanied by similar ones and the patient may survive for many years^{5, 6}. However, the prediction cannot be made that such a fortunate recovery will occur in any specific instance. The selection of cases



FIG 4—A Before operation showing site of metastatic lesion. B Photograph taken approximately five months after operation.

for removal of isolated metastases can only be made after determining that a) the general condition of the patient is good, b) there is no evidence of other metastases in the same or other systems, and that c) the lesion can be completely removed by a procedure unaccompanied by a prohibitive mortality.

Tantalum, a metal proven to be inert in human tissues, has recently received attention in the repair of bony defects, chiefly in the skull^{9, 10}. In addition, it has been used as wire, wire mesh, and tubes for arterial anastomoses. Paulson⁷ has used tantalum plates to cover chest wall defects but abandoned the method because of difficulty encountered in immobilizing the plate on a constantly moving structure such as the thorax. Griswold,³ in 1947, reported the successful temporary use of a tantalum plate as a prosthesis following resection of the body of the sternum for an osteochondrosarcoma. He found it necessary to remove it approximately two and one-half months later because of recurring hematomata. Griswold concluded that the method was a satisfactory procedure for a temporary readjustment period following operation.

A review of some anatomic facts may explain the successful use of the tan-

talum plate in the case reported 1 There is no motion between the first rib and the manubrium for a joint does not exist at this point 2 The second to the seventh ribs, inclusive, articulate directly with the sternum by means of true joints lined with synovial membranes 3 The seventh to the ninth ribs move between each other by means of interchondral articulations, but are anchored to the sternum through the sixth and seventh costal cartilages Thus, it is seen that the removal of the upper one-half of the sternum requires the sacrifice of only a few joints (in the case reported, three) and fixation of the ribs and sternum to a metal plate is correspondingly easier On the other hand, the substitution of a metal plate for the lower one-half of the sternum requires it to be an anchoring post for twelve or fourteen ribs Complications incident to motion of so many ribs upon a metal plate are easily understood Such a plate substituting for a portion of the sternum should probably then be limited to the superior portion of this structure, unless it is to be used, as Griswold suggests, as a prosthesis for a temporary postoperative period of readjustment

SUMMARY

- 1 Resection of the sternum for metastatic carcinoma in carefully selected cases is a feasible procedure
- 2 The use of a tantalum plate as a permanent prosthesis is more likely to be successful as a substitution for the upper one-half of the sternum than for the lower one-half
- 3 A case is reported in which such a procedure was successfully accomplished

ADDENDUM Since this article was submitted for publication, this patient has been seen monthly in the Out-Patient Department She was hospitalized for 12 days during October, 1948, at which time a small two-inch full thickness flap of skin and subcutaneous tissue was rotated over the right edge of the plate She was last seen January 25, 1949, one year after operation, at which time there was no evidence of recurrence or metastases and the prosthesis was solidly in place

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HYPERNEPHROMA METASTATIC TO THE THYROID GLAND

Report of a Case[†]

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HYPERNEPHROMA METASTATIC to the thyroid gland is so rare that only 20 cases are reported in the literature up to 1947 Linton *et al*¹ in 1946, in an extensive review of the literature, found only 15 proven cases and added one of their own In 1947 Boys² also reviewed the literature, found 15 cases and added a case report Each of these authors in his review found 1 reported cases not mentioned by the other A summary of these reviews is presented in Table I

CASE REPORT

L E, a man aged 48 years, was admitted to Albany Hospital on April 7 1942, with a chief complaint of fatigability, weight loss and the presence of a lump in the neck of 5 months' duration

About 5 months before admission the patient first noted a lump in the front of his neck which had not noticeably changed in size During this time he experienced increasing fatigability and listlessness In the few weeks prior to admission he became completely exhausted each day within one hour after arising in the morning Although his appetite remained unchanged he lost 20 pounds in weight He had increasing bouts of palpitation unassociated with dyspnea or ankle edema Although considered a nervous individual he did not complain of any change in this respect but did admit being more easily upset He perspired freely but did not like cold weather Review of systems disclosed no abnormalities other than the presence of nocturia 3 times per night

The past history revealed that 8 years previously, on May 18, 1934, he had a right nephrectomy A tumor in the right kidney was reported by the pathologist to have been a hypernephroma During his convalescence a course of deep roentgen-ray therapy was given in another city This treatment caused transient fatigue and low back pain Roentgenograms of the spine and of the pelvis in 1935 revealed no metastases For one year after nephrectomy the patient complained of urinary frequency and burning Eighteen months after operation, the patient was symptom free, had gained weight and felt completely well He was checked in the Out-Patient Clinic every 6 months for 2 years and once a year up to May 10, 1941 There were no further complaints until onset of symptoms 5 months before second admission

There was no family history of goiter, diabetes, nor tuberculosis

The patient was a well-developed man with evident recent weight loss The temperature was 97°, pulse 100, respirations 22, and blood pressure 104/68 The left pupil was slightly larger than the right but both reacted to light and on accommodation The extraocular movements were normal There was no exophthalmos nor widening of the

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palpebral fissures The trachea and larynx were deviated to the left by a visible mass in the right side of the neck The right lobe of the thyroid gland was enlarged, nodular, and contained one, large, particularly hard nodule at the lower pole The left lobe was slightly enlarged but not otherwise remarkable The large nodule in the right lobe moved freely on deglutition There was no thrill nor bruit

The lungs were clear to percussion and on auscultation The heart was not remarkable except for a few extra systoles There was a well healed nephrectomy scar in the right flank The liver was percussed 3 fingers below the costal margin

A roentgenogram of the chest revealed no evidence of metastases to lungs, the heart was slightly enlarged Hemoglobin was 17 Gm, red blood cells 663 million, color index 9, white blood cells 9,700 with 76 polys, 1 basophil, 20 lymphocytes, 3 monocytes Platelets appeared normal Urinalysis revealed no abnormality Blood Wassermann negative

Diagnosis—Non-toxic nodular goiter The possibility of a metastatic hypernephroma or other malignant lesion of the thyroid gland was considered

TABLE I

	Author	Year Reported	Number of Cases
1	Lubarsch	1894	1
2	Kodzubowski	1904	1
3	Barjon and Janiot	1912	1
4	Rost	1912	1
5	Pistocchi	1922	1
6	de Quervain	1924	1
7	Klose	1925	2
8	Kolodny	1926	1*
9	Willis	1931	1
10	Pemberton and Bennett	1934	2
11	Caylor and Caylor	1936	1
12	H Doubler	1936	2
13	Weiskittel	1937	1
14	Fey and Truffert	1938	1
15	Welti and Huguenin	1939	1
16	Long and Black	1945	1
17	Linton et al	1946	1
18	Boys	1947	1

* Questioned by Linton

On April 9, 1942, subtotal thyroidectomy was performed Anesthesia was novocaine infiltration, supplemented by nitrous oxide and oxygen inhalation anesthesia The thyroid was exposed through a low collar incision with midline division of the pretracheal muscles The right lobe of the thyroid was first elevated into the incision and found to be the site of hypertrophy with multiple, small, adenomata The superior pole lay posterior to the trachea The nodular masses were removed by resection of the right lobe and the capsule was closed The left lobe was found to be the site of a similar change and the same procedure was carried out as on the right The wound was closed without drainage The patient withstood the operation well and made an uneventful recovery

Dr A W Wright, head of the Department of Pathology, gave the following report on the tissue excised

Gross Description The specimen consists of one large and four small masses of thyroid gland which weigh together 24 Gm All of the masses are composed of dark reddish, typical thyroid tissue which is somewhat nodular with moderate amounts of colloid The largest mass contains, in addition, a fairly large, well outlined, pinkish-yellow, soft, homogeneous nodule which stands out from the adjacent thyroid tissue Other smaller but



FIG 1—Metastatic clear cell carcinoma of kidney origin occurring in thyroid gland



FIG 2--Primary clear cell carcinoma occurring in right kidney

otherwise similar nodules are present elsewhere in the largest thyroid mass and in most of the smaller ones

Microscopic Description Sections from this thyroid gland (Fig 1) show an adenomatous colloid goiter which is composed of small and large acinar groups, all of which contain colloid. The lining epithelium is generally low or flat.

In one section a totally different type of lesion is present. It is a fairly large, well outlined focus of neoplastic epithelial tissue which is composed of atypical cells growing in cord-like or alveolar fashion, often with lumens. In the latter situations the cells are oval or polyhedral in shape with distinct thin cell membranes and clear cytoplasm. Indeed, they appear to be little more than an empty space surrounded by a cell membrane. Each cell contains a dense spherical hyperchromatic nucleus which is centrally located, suspended, as it were, in an empty sac. Several large venous channels, into one of which a small tongue of tumor tissue projects, are present. About the periphery of the neoplastic focus there is a narrow, partially hyalinized, fibrous capsule which encircles part of the growth. This tumor is not characteristic of any primary thyroid carcinoma. Because of its strong resemblance to a primary renal carcinoma it is considered to be a metastatic clear cell carcinoma of renal origin.

Re-examination of the sections of the kidney (Fig 2) removed surgically from this patient in 1934 discloses the presence in that organ of a typical primary clear cell carcinoma. The neoplastic cells have clear cytoplasm, thin, distinct cell membranes, centrally placed hyperchromatic nuclei, and grow in cord-like or tubular fashion. The cells of the thyroid tumor resemble these renal carcinoma cells so strikingly that the present nodules in the thyroid are undoubtedly metastases from the primary renal growth.

Subsequent Course According to information received from the family physician, a growth as large as two fists appeared in the left side of the abdomen. Shortly after the appearance of this abdominal mass, death occurred, May 19, 1943, 13 months after thyroidectomy and nine years after removal of the kidney tumor. Permission for post-mortem examination was denied.

DISCUSSION

The case reported is one of six now in the literature in which metastatic hypernephroma appeared in the thyroid gland several years after nephrectomy for renal carcinoma. The metastatic nature of the thyroid lesions was, in each instance, discovered 7 to 13 years after removal of the renal tumor. In the case presented by Linton *et al*¹ the presence of hypernephroma in the remaining kidney at the time of thyroidectomy makes the primary source of the metastasis doubtful but in the other five cases the source could only have been the original hypernephroma.

Many of the cases reported were found only on necropsy. Since the thyroid gland is not routinely removed at many autopsies, it is reasonable to assume that more cases of metastasis to the thyroid gland from renal carcinoma have occurred than have been reported.

Because of the limited number of cases reported, no conclusions can be drawn. However, a metastatic hypernephroma must be seriously considered in those patients who develop a goiter following a diagnosis of hypernephroma. Since such metastases are known to have occurred as late as 13 years after excision of the original renal tumor, not even the passage of many years following the primary operation should rule out the possibility of such a diagnosis.

SUMMARY

A detailed case report of metastatic hypernephroma to the thyroid gland is presented and 20 cases found in the literature tabulated

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RETROGRADE INTRAGASTRIC INTUSSUSCEPTION OF THE JEJUNUM FOLLOWING SUBTOTAL GASTRECTOMY*

REPORT OF A CASE, APPARENTLY THE SECOND SUCH IN THE LITERATURE

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RETROGRADE INTUSSUSCEPTION of the jejunum following subtotal gastrectomy is so rare as to be a medical curiosity. A search of the literature reveals only one comparable case. It was reported by McNamara in 1944.

Case Report—JKW, white, male, age 55, was seen first on December 26, 1945. His chief complaint was stomach trouble. It began 18 years ago characterized by bloating and epigastric pain which was relieved by soda. His first hemorrhage occurred 13 years ago, the vomitus had a coffee ground appearance and the stools were tarry for several days. In recent months the patient experienced severe heart burn and often vomited small amounts of sour material with relief. On November 16, 1945, he had a gastric hemorrhage and was given a transfusion of 1,000 cc of blood. Pain and discomfort became more frequent after the hemorrhage, and was the reason for the patient entering the hospital. Roentgenograms over a period of years, done in Lexington and elsewhere, revealed a duodenal ulcer. In addition, during the past year the patient had nocturia 3 to 4 times and some dribbling. Eighteen years ago he had had a left inguinal hernia repaired and left orchidectomy, probably for an undescended testis. There was a recurrence of the hernia 6 years later. Appendectomy had been done 17 years ago. On 12-27-45, a subtotal gastrectomy was done by me for a recurrent, bleeding, chronic duodenal ulcer, and posterior Polya type of anastomosis was done. Convalescence was uneventful.

The patient re-entered the hospital 4-12-48 on the urological service of Dr. Douglas Scott, at which time his chief complaint was gradually increasing urinary frequency and difficulty in voiding. Since his stomach operation, he had only an occasional episode of upset stomach with slight vomiting. Urologic investigation revealed a bladder capacity of 8 ounces without residual. The KUB was negative, BUN 19 mg %, Rbc 4.6 million, Hgb 91%, urine negative. On 4-15-48 at 8:35 A.M. the patient went to the operating room for a transurethral resection. Spinal anesthetic was induced with 8 mg of procaine in glucose and spinal fluid between the 3rd and 4th lumbar vertebrae. One-quarter cc of neosynephrin was given, hypodermically, at the same time. The systolic B.P. ranged from 110-124-92-112 during the operation. A trilobar enlargement with ball-like median lobe was found. Twenty-seven grams of benign tissue was removed and a right vasectomy was done. Before the operation was completed the patient became nauseated and retched violently several times. Vomiting persisted at frequent intervals after the patient returned to his room. The vomitus was at first dark reddish-brown and later appeared to be bloody. This was accompanied by severe cramping pain localized to the ULQ. It was not relieved by morphine, $\frac{1}{4}$ grain. I saw the patient the following afternoon and examined him at 4 P.M. He stated that since his stomach operation he had been relatively free from indigestion except for occasional nausea and vomiting of clear material and infrequent heart burn.

Examination revealed an acutely ill patient. His skin was pale and clammy. He was vomiting small amounts of dark bloody, odorous material at frequent intervals and complaining of severe cramping pains in the ULQ. The temperature was 97°, the pulse was 90, regular and of good quality. The B.P. was 108/88. The abdomen in this rather

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INTRAGASTRIC INTUSSUSCEPTION

thin man was scaphoid and soft with slight tenderness in the U L Q. There was no rigidity, masses, or palpable organs. Upper right rectus, lower right rectus and left inguinal scars were present with a hernia in the latter. Clear urine was passing freely from the indwelling catheter. The R B C was 4.9 million and the Hgb 91%. Wangensteen suction was started and afforded the patient immediate relief. Blood, glucose, vitamins and amigen were given intravenously. For the next six days the patient continued to vomit at irregular intervals in spite of the indwelling intragastric tube which was in place most of the time. The vomitus was always a dark, foul, bloody material. The (R) temperature ranged from 99° to 100°. The pulse approximated 110. On 4-20-48 the leucocyte count was 18,100 with 72 polys. On 4-23-48 a barium meal was given which revealed a greatly dilated

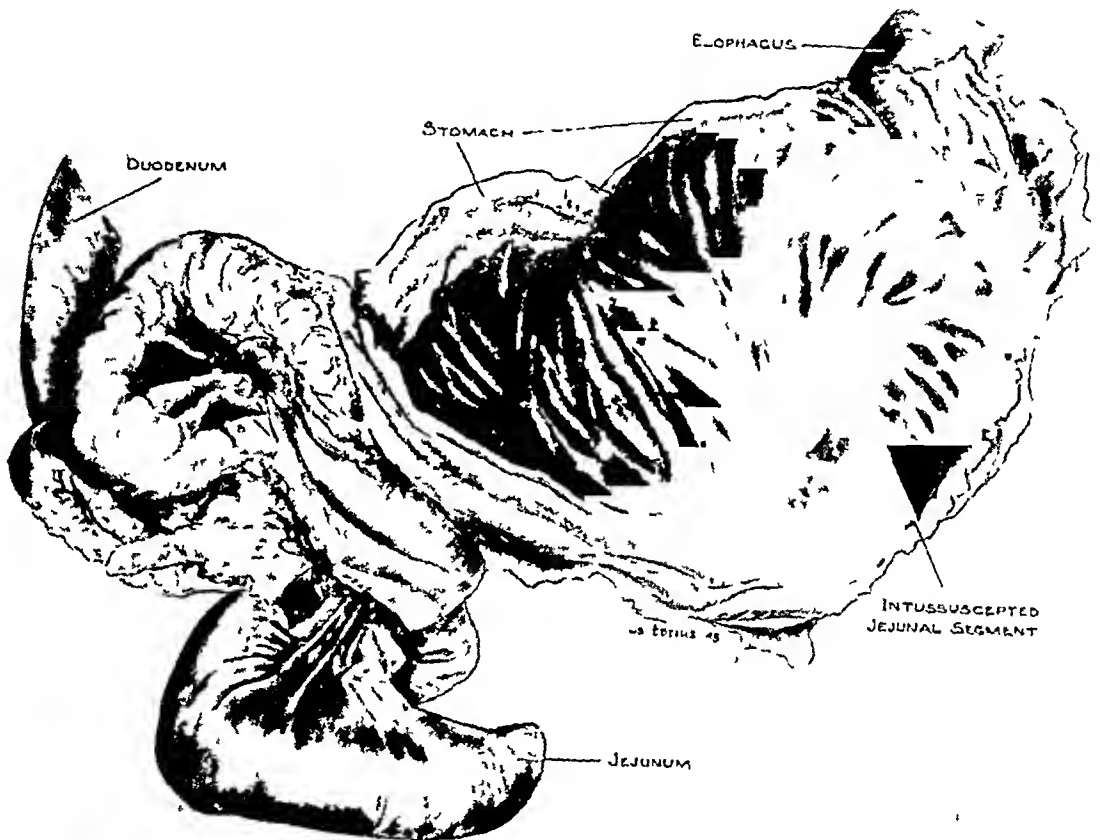


FIG 1—Postmortem specimen shows the opened stomach with the intussuscepted jejunum

stomach of which the distal half had been removed. There was a deformity which suggested a penetrating ulcer at the junction of the jejunum with the stomach. The 5-hour film showed 90% gastric retention.

On 4-24-48 the patient's condition became worse and an enterostomy was done under local anesthesia through a small upper left rectus incision. Feedings of milk, custard and amigen were given through the tube at 2-hour intervals. The patient's condition was unimproved and vomiting continued. On 4-27-48, in spite of four transfusions of 500 cc each of blood, the R B C was 3.4 million, the Hgb was 65%, the Wbc was 24,900 with 84% polys. At 5:30 P M the abdomen became very tender, rigid and distended in the upper one-half. The pulse became weak and imperceptible, the skin cold and clammy and the patient died at 11:50 P M.

Autopsy—The abdomen was somewhat distended. On opening the peritoneal cavity there was found four or five hundred cc of turbid, coffee colored fluid. Peritonitis extended from the pelvis to the under surface of the liver. The stomach was greatly

enlarged and when palpated a rough, soft mass could be felt within the lumen. The lower half of the stomach had been resected, and when the stomach was opened a large brownish black corrugated mass was seen. A retrograde jejuno-gastric intussusception of the efferent portion of the jejunum had occurred through the gastrectomy stoma, making a cylindrical mass measuring 17 cm in length and from 6 to 8 cm in diameter. The distal end was necrotic and dark in color. The portion of the small intestine below the intussusception was grossly negative. The site of the recent prostatic transurethral resection was not unusual.

Discussion—Intussusception is usually considered a disease of infants and young children. In these age groups it is one of the most important surgical emergencies. The process is often progressive and frequently without known cause. In adults the condition is usually brought about by some mechanical abnormality. In all age groups the direction of the intussusception is usually descending. According to Baumann there is one ascending to 200 descending types. In 1923 Drummond called attention to retrograde intussusception of the jejunum following gastro-jejunostomy. He reviewed the 11 cases previously recorded in the literature, two in England, nine on the Continent, and added his case which made 12 in all. His chief interest in the problem lay in the difficulty in explaining why it should occur in a few cases only and what steps could be taken in preventing it, or its relapsing as in the case of Baumann. He thought that occasionally rapid emptying of acid gastric content into the jejunum might result in forcible antiperistaltic action. The type of gastro-jejunostomy seemed to be of no consequence. In the first 12 cases reviewed, five were the anterior type, five were posterior type and no mention was made of the type in two cases. Enteroanastomosis had been done in five of the 12 cases. With the increasing popularity of gastro-jejunostomy in the treatment of peptic ulcer by 1935, Debenham was able to collect 35 cases of retrograde intussusception of the jejunum and added a case to the series. He was surprised that this complication was not reported until 1917, although gastro-jejunostomy was first performed in 1881. In the recorded cases the incident occurred from six days to 16 years after the original operation. The length of involved segment varied from 4 cms to 2 metres and the type and size of the stoma apparently played no part in initiating the process.

Chesterman thought that the condition was of sufficient interest to warrant record by virtue of its rarity, the ease of diagnosis if its possibility is remembered, and the hopeless prognosis without early surgical intervention.

According to the collected reports the symptoms seem to follow a rather definite pattern. Following at variable periods after gastro-jejunostomy there is a sudden onset of cramp like upper abdominal pain which frequently doubles the patient up. This is followed by vomiting, first of food and bile and then bloody fluid. As the pain and vomiting continue the patient's skin becomes pale and clammy. Rigidity and distention do not appear early, nor is tenderness constant. The presence of a soft tumor in the upper abdomen has been noted in about one half of the reported cases. Early surgical intervention with reduction of the intussusception or resection has yielded good results.

Sufficient interest has been aroused and attention focused on retrograde

jejunogastric intussusception so that each year finds new cases added to the increasing number recorded in the literature. A very careful search, however, reveals but one case comparable to the one I report. In 1944, McNamara reported the first case of retrograde jejunogastric intussusception through a subtotal gastrectomy stoma. So far as I can determine, the present case is the second such appearing in the literature. The etiology is speculative. However, since the onset was sudden and acute during an operative procedure one is inclined to carefully evaluate the anesthetic and the operation for contributing or precipitating influence. It is an accepted fact that patients receiving a spinal anesthetic may become nauseated and vomit. A transurethral resection rarely, if ever, initiates vomiting. I believe it more reasonable to attribute the vomiting in this patient to the anesthetic agent. Since it was so violent it is most likely that it was the influence in precipitating the retrograde intussusception. The repeated vomiting indicated a high obstruction, but the cause of the foul, bloody vomitus was erroneously deduced. In view of the past history of gastric resection for a bleeding ulcer and the subsequent, although mild recurrence of dyspepsia, the condition was first attributed to an obstructing, bleeding, marginal ulcer. Because of the high resection the remaining segment of stomach was beneath the thoracic cage and a tumor was never felt.

The explosiveness of the symptoms in the now two reported cases of retrograde jejunogastric intussusception through the gastric stoma are quite similar to the same process in the more frequently occurring intussusception following gastro-jejunostomy. Characteristics are the sudden onset of severe cramping abdominal pain, persistent vomiting of bloody material, shock and in some cases the presence of a soft tumor in the upper abdomen. If the condition is known and its possibility is remembered the diagnosis should not be too difficult. The prognosis is hopeless without early surgical intervention.

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WANDERING SPLEEN*

REPORT OF A CASE COMPLICATED BY A TRAUMATIC CYST

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WANDERING SPLEEN IS VERY RARE, as shown by statistics of a large number of splenic diseases published by various authors Whipple (1945)³³ reported a series of 1,437 cases of splenic diseases seen at the Combined Splenic Clinic of the Columbia Medical Center over a period of 10 years, the series included about 20 different diseases of the spleen, but not a single case of wandering spleen Among 1,003 splenectomies done at the Mayo Clinic over a period of 40 years (1904-1945), wandering spleen was present in two cases only, and both occurred before 1934^{13, 25} Most of the reported cases were complicated by torsion of the splenic pedicle, and the following case is interesting as it shows the association of another complication, so far not reported in the literature, namely, traumatic subcapsular blood cyst

CASE REPORT

S S J, female, aged 51 years, married, had 2 children, was admitted to the University Hospital, Alexandria, on Nov 11, 1946, complaining of a mobile swelling in the left side of the abdomen, continuous dragging pain in the region of the stomach, sense of distention, occasional attacks of vomiting following heavy meals by 1 or 2 hours, (the food being vomited unchanged), and splashing sounds in the stomach after drinking water These symptoms were present for the last 4 months Five months before the date of admission, *i.e.*, one month before the onset of the present complaint, she was kicked in the left upper part of her abdomen by a donkey, the kick was so severe that the patient fell on her back, hit her head on the ground, lost consciousness, and was carried home She came around 2 hours later, and immediately after that she felt severe colicky pain at the site of the trauma associated with frequent vomiting, the first vomit contained red blood For the following 3 days the patient was in a semidrowsy state, and the vomiting and pain continued She was forced to stay at home in bed for 13 days, after which her condition improved gradually No signs of injury of the abdominal wall at the site of the trauma was noticed by the patient One month after the date of the accident she first noticed a small mobile swelling below the left costal margin, which was slightly tender to her touch The swelling gradually increased in size, and was associated with repeated attacks of localised pain which radiated to the left loin The dragging sensation and the gastric discomfort developed gradually The general health of the patient suffered as a result of restricting her diet so as to avoid the vomiting and the pain Nothing of importance was found in her past history except that four years ago she developed an irregular fever which persisted for about one month, the fever subsided without medical treatment, and did not recur After a short time she noticed ill-defined pains in the left hypochondrium which passed off within a few days She was quite normal up to the date of the accident The family history is of no special importance

Physical Examination showed a moderately built and nourished female subject, with normal features, P 80, T 37, R 24, B P 150/100 The abdomen showed redundant and inelastic skin in the lower half, flabby and weak muscles, wide subcostal angle, and absence of dilated or varicose veins in the abdominal wall There was a swelling easily

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seen by inspection while the patient was standing, but better still when she was lying on her back. The swelling occupied the left lumbar, lower part of left hypochondriac, and left part of umbilical regions, it was globular, 15 cms in diameter, cystic with free fluctuation, smooth on the surface, and with a definite contour. On deep palpation, it was found that this cystic swelling overlay and was fixed to an enlarged spleen, the lower pole of which reached the left iliac fossa, while the rounded upper pole was felt below the left costal margin and was easily grasped by the hand. The anterior border of the spleen was sharp, with two notches on it, while the posterior border was rounded, smooth, easily felt, and it was possible to lift the whole spleen up by insinuating the hand behind it. The cyst and the spleen moved with respiration, and it was possible to move them together to the right side of the abdomen until they filled the right lumbar region, where they stayed for a while, then gradually returned to the left side. This movement was painless. When the patient lay on her right side the swelling fell beyond the middle line. The spleen was movable down so far that its lower pole disappeared behind the symphysis pubis, but it was not possible to push it up beneath the costal margin as the cyst bulged very much anteriorly. The cyst was slightly tender on deep pressure, dull on percussion, but loops of small intestine came in front of the spleen to surround the cyst, so the rest of the splenic surface was resonant. The area of normal splenic dullness was absent. A band of resonance was found between the upper pole of the spleen and the costal margin, and a similar area was detected between its posterior margin and the outer border of the left sacrospinalis muscle. The liver was firm, smooth, and its lower border felt 4 fingers below the xiphoid process, and the upper border was in the fifth intercostal space (i.e., the liver was not ptosed). The lower pole of the right kidney was palpable, and the rest of the abdomen was free. It was evident that the spleen had altered its relations so that its diaphragmatic surface now faced antero-laterally, and its anterior and posterior margins faced medially and laterally respectively. The case was diagnosed enlarged wandering spleen, with a traumatic subcapsular cyst on the diaphragmatic surface. Splenectomy was decided upon.

Laboratory Data

Urine acid, alb +, sugar—, pus cells++, Bilh ova+

Stools positive for ascaris ova

Blood urea 38 mgs %

U C T fasting before urea—

	0.6 Gm %
first hour	90 cc 0.8 "
second hour	110 cc 1.0 "
third hour	100 cc 1.2 "

Blood picture Hb 70%, R B C 3,900,000, W B C 5,400, (eos 7%, polym 58%, mono 30%, bas 0%) negative for malaria

W R neg

Radiography Stone pelvis of left kidney, (this was found to have passed to the ureter after 6 months)

No definite soft tissue shadow of the spleen, or of the cyst was seen in a plain roentgenogram of the abdomen. No signs of calcification in the cyst. Thorotrast injection was not done, nor a barium meal or enema.

Operation Dec 15, 1946, by Prof Abbas Hilmy

Blood transfusion of 1,000 cc was given before the operation. Under light percaïne spinal anesthesia the abdomen was opened by a left upper paramedian incision. On opening the peritoneum the anatomy of the condition was obvious. The spleen was found in the centre of the abdominal cavity, its costal surface turned forward, and over it, near the lower pole, a big brown coloured cyst with smooth shining wall. The cyst was tense and measured about 15 cms in diameter. The surface of the spleen was smooth, and its upper pole lay well below the left costal margin. No adhesions were attached to the



FIG 1—Photograph of patient before operation. A Splenic cyst in the resting state, the patient lying on her back. B The spleen has been pushed to the right side of the abdomen, and the picture taken immediately after the hand was removed. C Lateral view of the abdomen to show the bulging of the cyst anteriorly, it was not possible to push the spleen back under the costal margin.

spleen, except for the thin stretched phrenico-splenic ligament, which was cut and the spleen easily delivered. The splenic pedicle was long, thin and broad, and the tail of the pancreas was free from it. The gastro-splenic ligament was longer than usual, and was cut between ligatures. The main pedicle was excised in sections between ligatures on the proximal side, and clamps on the splenic side. After the spleen was removed with the clamps on, the ligatures on the pedicle were reinforced by another series of similar ones. The rest of the abdominal organs were inspected and were found normal except for the stomach which was dilated and ptosed, and the transverse colon which was unduly

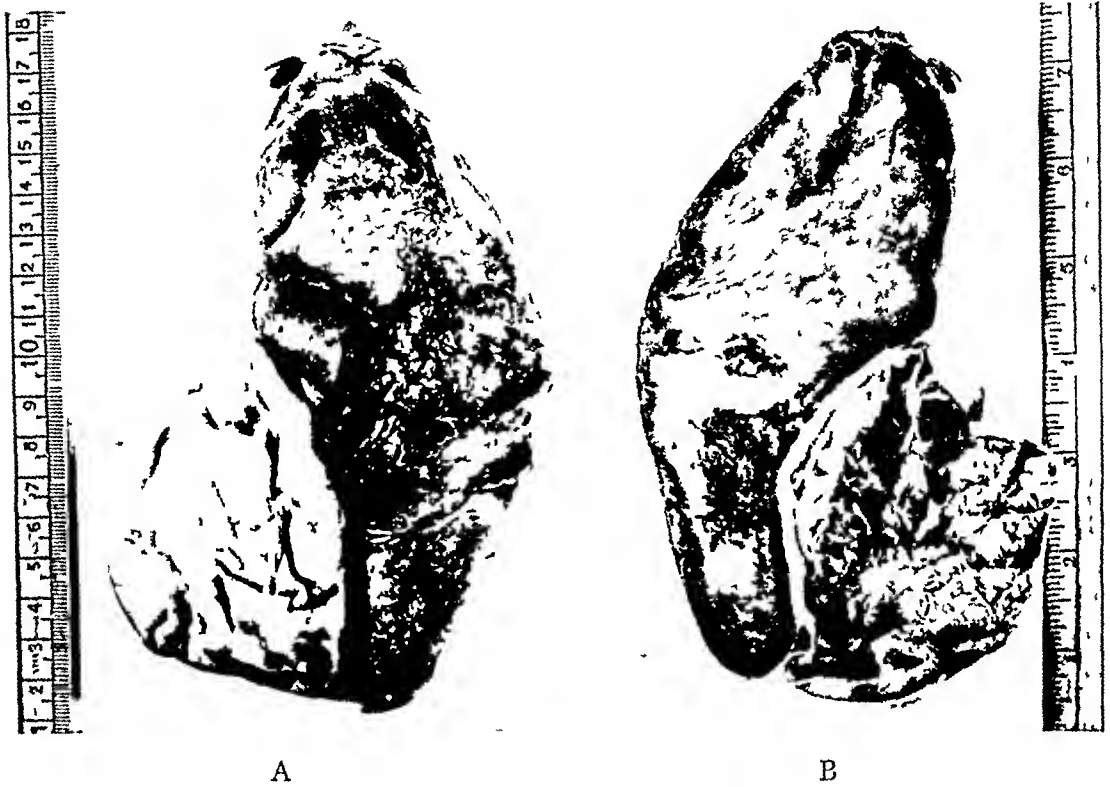


FIG 2—Specimen of the spleen with the cyst on the lower part of the costal surface, the picture was taken after the spleen has been hardened in formalin, showing a relative reduction in its size A Costal surface B Cut section

mobile. The stone in the left kidney was not dealt with, and the abdomen was closed in the usual manner. The removed spleen weighed 1,200 Gm, it was 25x15x15 cm in dimensions, the diameter of the cyst 15 cm, and contained about 300 cc of a thin brownish fluid. The inside wall was full of fibrinous trabeculae.

The patient passed through a smooth uncomplicated postoperative course, and was discharged fit on the 12th day, with a good sound scar. She was seen 2, and 16 months after the operation, was found to be in very good health, and her previous complaints completely disappeared.

Pathologic Report (By Prof. Gazayerly) Spleen (after evacuation of blood and being hardened in formalin) weighs 750 Gm, there is a cyst about 7 cm, containing fibrin, and some blood. The peripheral wall of the cyst is very thin and about 1 mm thickness but where it is attached to the spleen over an area of 8 cms the wall is thick (0.5 cm), and is made of greyish white fibrous tissue. On section the splenic tissue is deeply congested and the Malpighian bodies are rather inconspicuous. Microscopical examination showed that the white pulp is greatly encroached upon by the congested red pulp. The sinuses of the red pulp are distended with blood. The splenic arterioles show

marked thickening of their walls with hyaline degeneration. The wall of the cyst is made of fibrous tissue. The picture is consistent with Egyptian splenomegaly and a blood cyst. It is quite possible that the blood cyst has resulted from an organised hematoma.

COMMENT

This case is interesting because it presents the two most uncommon conditions of the spleen, namely, the wandering state and cyst formation. The enlargement is due to the condition called Egyptian splenomegaly, an endemic disease in Egypt, related etiologically and pathologically to bilharzial infection of the alimentary canal^{1, 11, 18, 19, 20, 26, 29}. It is one type of congestive splenomegaly due to bilharzial cirrhosis of the liver, the spleen as a result of portal congestion undergoes considerable hypertrophy. Such spleens always tend to get fixed in position by a process of perisplenitis giving rise in some cases to very dense adhesions between the spleen and the diaphragm. During the operation of splenectomy these must be cut by the hand, scissors, or between clamps, some cases are even impossible to remove on account of a process of complete cohesion between the spleen and its bed. The condition usually remains silent until the spleen is so enlarged as to produce signs and symptoms due to its mechanical effects. The organ is usually fibrous and firm, rupture of Egyptian splenomegaly is therefore rare as compared with rupture of malarial spleens. The enlargement in this case was associated with a good range of abnormal mobility which saved the spleen from a complete tear as a result of the comparatively severe kick, (a trauma which most probably would rupture a normal spleen, or more easily an enlarged fixed one). An anterior subcapsular rupture occurred which organised into a hematoma, within four months this developed into a false blood cyst. The stomach also suffered from the kick as evidenced by the hematemesis. The resultant increase in weight of the spleen increased its range of mobility and started the various symptoms which were mostly due to the mechanical dragging on the stomach. It is questionable whether the trauma had directly affected the mobility of the spleen by tearing its supporting ligaments.

DISCUSSION

The normal spleen has a very limited range of mobility. Fowler¹² has studied this in many laparotomies, and found that the normal spleen has excursions not exceeding $1\frac{1}{2}$ inches. The factors which keep it in its usual place in the upper abdomen are the general intra-abdominal pressure, and the various peritoneal reflections or ligaments which fix it to the surrounding structures. The two chief and strong ones are the phrenico-splenic ligament (often not mentioned in anatomy books), and the lemo-renal which contains in between its two layers the pedicle of the spleen and the tail of the pancreas. The others, namely, the gastro-splenic, splenico-colic, and phrenico-colic ligaments are usually weak and inconstant in development. The latter is, however, considered by some authors as the chief support, acting as a hammock over which the lower pole of the spleen rests, so often called the sustentaculum lemnis. Disturbance of this supporting mechanism will allow the spleen

to descend in its bed, and to acquire variable degrees of mobility in the abdominal cavity. Congenital factors, as absence of the supporting ligaments, a long mesentery, or a very narrow upper abdomen, account for some cases². On the other hand, the majority of cases are due to acquired conditions, either increasing the weight of the spleen as in cases of splenomegaly, tumors or cysts, or reducing the intra-abdominal pressure, as after repeated pregnancies, or in visceroptosis¹². The value of these several etiologic factors has been discussed by various authors, and more than one factor may be working in individual cases.

Clinically, the condition may be symptomless, and the spleen discovered accidentally in abnormal places in the abdominal cavity or pelvis. In some cases, especially if the organ is enlarged, dragging on the stomach or transverse colon interferes with their motility or blood supply, and so produces various gastric or intestinal symptoms. The majority of patients however seek surgical advice on account of the presence of associated complications. Axial rotation of the spleen may occur leading to torsion of its pedicle, which may be acute, chronic or recurrent^{2, 3, 4, 9, 31}. In acute torsion the pedicle may twist many times, occlusion of the splenic vessels will result, and if the spleen is not removed hemorrhagic infarction of all or part of the organ will occur. A degenerative cyst may develop as a later complication. In severe cases the spleen will become gangrenous and if sepsis is superimposed a splenic abscess, localised or diffuse peritonitis will result. The included tail of the pancreas may slough with the spleen³. Associated acute intestinal obstruction may develop, in some cases due to inclusion of loops of small gut among the twists of the pedicle, in others due to adhesions and pressure of the twisted organ on the large gut, in still another group the spleen was already adherent to the pelvic colon, and when twist of the spleen occurred, a resultant volvulus of the pelvic colon developed^{2, 15, 28}. Chronic or recurrent torsion will induce in the spleen a state of chronic venous congestion, leading to hypertrophy, perisplenic adhesions, or cyst formation. The spleen in its wandering may become fixed in abnormal places as the pelvis, right or left iliac fossae, there it may enlarge, become impacted, or press on the surrounding viscera, as the sigmoid colon, uterus or bladder, and there produce symptoms referred to them^{6, 28, 31}.

The treatment of the condition is splenectomy, the old operations of splenopexy, or detorsion and splenopexy in cases of torsion have no place in modern surgical practice.

SUMMARY

A case of an enlarged spleen showing excessive mobility is reported, the enlargement is secondary to Bilharzial cirrhosis of the liver which was early and of the fine type. The condition was symptomless until the patient received a blow which caused a subcapsular rupture on the costal surface of the spleen, which later developed into a false blood cyst, and so, by adding to the weight of the spleen started to produce symptoms.

I wish to express my thanks to Prof. Abbas Hilmy for his kind advice and help, and for permission to publish this case.

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BOOK REVIEWS

"NEUROANATOMY," by Fred A. Mettler, M.D., St. Louis, C. V. Mosby Company, 2nd Edition, 1948 \$10.00

The 2nd Edition of this comprehensive textbook of neuroanatomy maintains the same general organization as the previous edition although some sections have been expanded, resulting in an increase to the text of 60 pages. The material has again been divided into two sections, the first dealing with gross aspects of the nervous system and the second with microscopic anatomy.

The section on the gross aspects of the central nervous system is only slightly modified from the previous excellent presentation of general relationships. New material has been added on the arterial supply and venous drainage of various portions of the neuraxis and the illustrations have been amplified. This section is largely descriptive and serves as a very valuable orientation of the macroscopic form of the central nervous system for all those dealing with this field. The excellent additions regarding the blood supply of the thalamus, basal ganglia and other structures are of great importance and the description of the relationship between the topography of the brain and that of the skull and extra-cranial structures continues to be valuable from the clinical viewpoint.

The second half of the book deals with the microscopic anatomy of the central nervous system, starting with the spinal cord and ending with the cerebral cortex. This material is profusely illustrated with drawings showing the main fiber tracts accompanied by a similar drawing showing the cell populations at that same level. This information is then summarized by various types of diagram which clarify the position and function of certain of the main tracts and association systems. The microscopic structure and function of the diencephalon are dealt with in great detail and this is supplemented by actual photomicrographs of sections of the thalamus which were not present in the previous edition. The relation between the various thalamic nuclei and the various areas of the cerebral cortex are also described in some detail, this being based on work which is not as yet complete. It might have been advantageous to summarize the known projections in text and diagram and omit some of this detail at the present time. Throughout this second section of the book, there has been a strong effort to try and correlate function and structure which serves to increase the usefulness of the material.

In spite of the detail with which the corpus striatum and diencephalon are described, both as regards form and what is known of function, the cerebral cortex is covered in a very scanty section with no mention of the large volume of recent work which correlates function of the various cortical areas with their structure both in man and the experimental animal. In addition, certain of the physiologic correlates of diencephalic structure and of the extrapyramidal system do not take into account a fairly large segment of recent work which would alter the emphasis which the author has placed on the quoted evidence.

This text continues to be one of the most complete in its field and, in spite of certain minor errors, represents an outstanding reference work. Because of the mass of intricate detail presented, however, its usefulness to clinicians is impaired.

ARTHUR A. WARD, JR., M.D.

THE HOSPITAL CARE OF NEUROSURGICAL PATIENTS, 2nd Edition, by Wallace B. Hamby, M.D., F.A.C.S., Springfield, Ill., Charles C. Thomas, 1948 \$3.00

This little volume, which has recently come out as a second edition, should be a "must" on the reading list of all nurses engaged in the care of neurosurgical patients. There is also much in it of profit to the average interne and resident involved in pre- and postoperative neurosurgical care. The book is written in an easy, direct manner and,

while no attempt has been made to be complete to the last detail, all of the important points of pre- and postoperative care of neurosurgical patients are very adequately covered

There is an especially good discussion on the relationships of the house officer to the patient, his relatives, and other members of the hospital staff, outside his immediate domain. It is noteworthy that the author points out that Cushing obtained necropsies in over 90 per cent of his cases and that one of the major duties of all concerned with the neurosurgical patient is the absolute necessity of obtaining necropsies.

The author starts with a relatively simple review of the fundamentals of gross neuroanatomy and proceeds to describe all the minor procedures in neurosurgery from venipuncture to ventriculogram. The paragraph on the technic and importance of cisternal puncture is particularly recommended. There is a very adequate discussion of the importance of arteriography and the means and methods of performing the Matas Test and carotid obliteration, before considering any type of ligation of the carotid. The author also elaborates on the use of catheters and the significance of good care of the genitourinary tract in neurosurgical patients, particularly those with spinal cord damage. Two relatively minor omissions were first, the lack of discussion of the Penrose drain for adequately and simply controlling male micturition and second, the omission of the more modern method of the Munro set-up for tidal drainage, which obviates the use of much of the tubing and the old reservoir described by the author from the original Munro diagram of 1935. The discussion of the postoperative care of craniotomies and suboccipital craniectomies is particularly good in covering all the minute details so important to the young nurse and interne learning the "why's and wherefore's" of head dressings. A questionable omission is the use of gloves for *all* neurosurgical dressings, which we feel has cut down the incidence of infection to some extent at least. Although, in his introduction, Doctor Hamby stresses that he intends in no way to be specific concerning the use of antibiotics, the small section of one and three-quarter pages devoted to wound infection appears somewhat brief, especially when frequent laboratory studies, with cell counts and bacterial sensitivities, play such a prominent part in infection of the central nervous system. The frequency of lumbar puncture advised by Doctor Hamby is to be questioned somewhat and particularly its role in the immediate postoperative days following drainage of brain abscess. However, this is a matter to be decided only by the chief of the clinic and assumes different importance in various centers. The preoperative care of lobotomy is good, with much emphasis on the subsequent psychiatric care following operation while in the hospital. Again, the significance of frequent notes by the nursing staff and adequate psychotherapy are well stressed.

The size of this book and its readable print lend additional qualities to make it required reading for any group of students about to enter this specialized field. The book is completely indexed and the black and white illustrations by the author make all the procedures and anatomical points described readily understandable. We feel that Doctor Hamby has very ably accomplished that which he set out to do, namely, to supply a useful handbook which would be readily available on the floor nurse's desk for consultation by all house officers and nurses.

FRANCIS C. GRANT, M.D.

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No 4



A PRELIMINARY REPORT ON THE ADVANTAGES OF A SMALL STOMA IN PARTIAL GASTRECTOMY FOR ULCER*

BY H W PORTER AND Z B CLAMAN

EDINBURGH, SCOTLAND

IN THE TREATMENT OF CHRONIC PEPTIC ULCERATION, it is now generally accepted that partial gastrectomy consistently gives the most satisfactory results. Although the results on the whole have been satisfactory, inasmuch as the predominant symptom—pain—has been relieved and the chances of stomal ulceration greatly reduced, there is no doubt that gastrectomy has often left the patient with other less severe disabilities. We feel that many of these can be almost completely eliminated by a minor modification in the type of operation carried out.

Clavel⁵ and many others believe that the most physiological type of gastrectomy is the Hofmeister-Finsterer operation. This operation has certain advantages attributable to the valve which is made to prevent regurgitation of food into the duodenum.

Many believe that the size of the stoma has no effect on the final results of the operation and this assumption is largely based on the experimental work of Mehring and McCann.⁸

Hofmeister recognized the danger of leakage occurring at the upper angle of the anastomosis of a full length gastro-jejunal stoma after sub-total gastrectomy, and in order to avoid this leakage and thus reduce his mortality rate, he advised the infolding of the upper end of the gastric remnant for 2 or 3 cms.

Finsterer² made the observation that unpleasant symptoms after gastrectomy often occurred as a result of the reflux of gastric contents into the afferent jejunal loop. Wright³ in 1929, described two cases where barium could be seen entering the proximal duodenal loop, and both these cases complained of discomfort. Ogilvie⁴ in 1947, stated that this reflux is the commonest cause of postoperative discomfort. Finsterer's early recognition of this cause of postoperative discomfort led him to advocate the closure of the upper part of the gastric remnant, so as to leave 10 cms. of the lower end open. The valve so formed was intended to prevent reflux into the afferent loop, in addition to making the anastomosis safer from leakage.

One of the authors (P) undertook to make the stoma much smaller than is usual in order to increase the emptying time.

* Submitted for publication, October, 1948

Since emptying time appears to have direct bearing on the clinical end results, as shown by Strauss⁶ and others, we have carried out a series of cases making the stoma much smaller than is usual in an endeavour to delay emptying time. Mehring in 1897, from experimental work with dogs, concluded that the pyloric sphincter does not control the emptying time of the stomach, and after its removal the emptying time of the remnant is the same as that of the intact stomach. Since then, others have repeated his experimental work, and confirmed his results. McCann⁸ 1939, repeated this experiment and came to the same conclusions but added the important fact that the quantitative emptying time is definitely affected, and showed that although the total emptying time remains the same after the removal of the pyloric sphincter, the quantitative emptying time is reduced. In other words, the volume of the gastric residue 30 minutes after a meal in the resected stomach, is much less than that in the intact stomach. This latter observation appears to have been ignored by most writers on the subject, with few exceptions. Shay and Gershon-Cohen⁹ recognized this factor, making a clear differentiation between the total emptying time, in which the pyloric sphincter plays very little part, and the quantitative emptying time, in which the sphincter plays a definite role. Thus theoretically, if a sphincteric-like action could be obtained at the gastrojejunal stoma, the likelihood of a delayed quantitative emptying time should be increased, although the total emptying time might remain unaffected.

McCann⁸ from experimental work on dogs in which he resected increasing amounts of stomach, connecting the gastric remnant to the small intestine, came to the conclusion that the size of the stoma had no relation to the emptying time of the gastric remnant. Ravdin¹¹ and others came to the conclusion that the new stoma, regardless of size, is not the reason for the rapid gastric emptying. By these statements, various writers in the literature have confirmed the impression that the size of the stoma will not control the emptying time of the gastric remnant. Recently Kennedy, Reynolds and Cantor¹² have pointed out that the factor which controls emptying time of the stomach is not the size of the stoma but the size of the jejunal lumen. This, however, only applies when the size of the stoma is greater than the size of the jejunum, and also presumes that the stoma has no sphincteric action.

Recognizing these facts, we have made a stoma 2.5 cm. in length in a series of 118 sub-total gastrectomies for ulcer. The indications for operation have been

Repeated Perforations—

1	—	30 cases	
2	—	7 cases	
4	—	1 case	— 38

Hemorrhage—

Acute Massive	—	8 cases	
Multiple	—	9 cases	— 17

<i>Failed Medical Treatment</i>	—	63	118
---------------------------------	---	----	-----

and we have found the following advantages

- (1) *The advantages of the Hofmeister-Finsterer Valve*
 - (a) Decreased incidence of leakage at the upper end of the anastomosis
 - (b) Decreased incidence of retrograde influx into the proximal jejunal loop
- (2) *Bulging of the jejunum after food is prevented*



FIG 1—A X-ray showing the bulging of the jejunum (J) opposite the wide anastomosis after a Polya gastrectomy

Kennedy, Reynolds and Cantor,¹² in a review of 90 cases of Polya type of gastrectomy, found a uniform roentgen ray finding of jejunal dilatation and show a post-mortem specimen drawing, which clearly indicates the jejunal dilatation that occurs with the wide gastro-jejunal type of stoma (Fig 1). They say that this jejunal bulge prevents the patient from eating a normal volume of food and is one of the causes of postprandial discomfort—with this we are in full agreement. This tendency to bulging was also recognized by Vitkin,⁷ Gordon Taylor¹³ and others. In our series, where 90 cases have been followed up radiologically, there was no jejunal bulge in 84 cases, and only slight fullness in six. In no instance was the jejunal bulge present to the degree indicated by Kennedy¹² *et al*.

(3) *The risk of postoperative hemorrhage is diminished*

The source of hemorrhage after gastrectomy is from the cut edges of jejunum and stomach. As the jejunum is only incised for a length of $2\frac{1}{2}$ cms the risk of hemorrhage is correspondingly reduced. Allan and Welch¹⁴ in a series of 151 cases of gastrectomy with long stomas reported four fatal hemorrhages. Reinhoff¹⁵ reports 10 per cent of hemorrhage (non-fatal and fatal) occurring after a Polya type gastrectomy in 260 cases. In this series of 118 cases, there has been no case of serious hemorrhage from the stoma, six cases had slight hemorrhage but these improved with conservative treatment.

(4) *Increased emptying time*

The normal stomach empties in $3\frac{1}{2}$ –4 hours using a water barium sulphate mixture. It has been shown by Ravdin¹¹ that varying the solution will affect the emptying time. Vitkin⁷ states that the average emptying time after gastrectomy is 20 minutes, and quotes various European authors who point out that the emptying time may be much less. Shay and Gershon-Cohen⁹ believe that the decrease in emptying time following gastrectomy is the direct result of achlorhydria. They show that in no cases of gastric resection does the emptying time exceed 30 minutes.

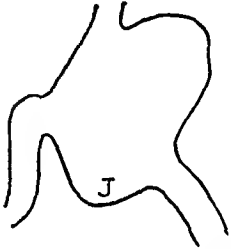


FIG 1 — B Line drawing showing the bulging of the jejunum (J) opposite the wide anastomosis after a Polya gastrectomy.

Gilbert and Dunlop¹⁶ say that it is a well established fact that the gastric remnant empties quickly and that the rate of emptying is increased following a carbohydrate meal. It is interesting to note that the intact achlorhydric stomach empties in 15–90 minutes. Strauss⁶ and others reported 25 cases of gastrectomy in which 25 per cent emptied in 15–20 minutes. They state that the slower the emptying time, the better is the clinical end result. It must be noted, however, that the total emptying time was used, no estimation of quantitative emptying time was made.

Quantitative emptying time may be defined as the period taken for the fluid level in the gastric remnant to disappear after a barium meal. Flakes of barium which may be seen adhering to the mucosa after a meal, are disregarded.

In this series in which 40 cases were followed, the average quantitative emptying time was 58 minutes. Only three cases in this series had quantitative emptying time of less than 30 minutes. Two of these cases were followed up one month after operation and the remaining case one year after operation. Eight cases had an emptying time of 30–40 minutes and the remaining 29 cases had an emptying time exceeding 45 minutes. Of these, five cases were followed up less than six weeks after operation and five cases less than three months.

(5) *Sphincteric-like action of the stoma*

Schindler¹⁷ on following up 52 cases of a Polya type gastrectomy, found that on gastroscopic examination, 48 of the cases had a rigid type of stoma which remained patent throughout. In these cases there was considerable edema with inflammatory change and erosion of the gastric and jejunal mucosa. In only four cases was there a sphincteric-like action at the stoma and these four cases were the only ones with a healthy mucosa and which were

entirely symptom free. We think that the sphincteric-like action is due to contractions of the jejunal musculature rather than that of the stomach, as the first swallow of barium passes straight through the stomach into the jejunum (Fig 2A) which then contracts and closes the stoma. The stomach then fills (Fig 2B) and as the jejunum, having emptied, relaxes, more barium flows through the stoma. In 88 per cent of the cases in our series there was roentgenologic evidence of this sphincteric-like action, which usually appeared within six weeks of operation.

The prevention of jejunal bulging and the increased emptying time encourage the early resumption of a normal diet postoperatively. The psychologic effect of a diet, normal in quantity, cannot be over-emphasized. In this series, fluids—milk or sweetened drinks—were given within 12 hours of operation, and within 10 days the patients were receiving a normal hospital diet. This has an important effect in convincing the patient that he has now a healthy stomach. The patient leaves hospital with specific instructions to eat and drink anything he wishes. The vast majority of our patients have been ready to follow these instructions. Of the 112 patients followed, all except two have returned to their former employment, these two having been off work for 15 years before operation. We have also found that weight gain is much more rapid if a normal diet is returned to at an early date, and that there is a very low incidence of post-gastrectomy anemia. If a wide stoma is used, it is generally accepted that frequent small meals and prolonged postoperative medical care with a comprehensive but concentrated diet are desirable. With a small stoma, this careful postoperative care is eliminated.

The reasons for these advantages are

(a) The stoma functions immediately (Fig 3)

We have several roentgenograms taken between 12 and 24 hours after operation which show the passage of barium through the stoma. Allan and Welch¹⁴ record eight cases of obstruction with a full length stoma in a series of 151 cases. In our series there has been one case.

(b) With the early sphincteric-like action of the stoma, there is rapid dilatation of the gastric remnant and delayed emptying time. This was shown in 60 cases, x-rayed 4–6 weeks after operation, in which the gastric remnant had the capacity approximating that of a normal stomach. Vitkin⁷, who reviewed 45 cases with wide stomas, found that in the first three months six had an average sized gastric remnant and in all of the remainder the gastric remnant was high and small. Strauss⁶ *et al*, discussing the size of the gastric remnant after resection of two-thirds of the stomach, observed that 69 per cent of the remnants remained the same size, 17 per cent decreased and 14 per cent increased in size, and made the statement that the slower the emptying time the better the clinical end results. In 13.2 per cent of the cases in our series the gastric remnant remained the same size and in 86.8 per cent the size was increased. None of the cases showed decrease in size.

(c) Another asset of the small stoma is that it prevents jejunitis by protecting the jejunum from immediate contact with food over a wide surface. Schindler¹⁷ demonstrated jejunitis in 92 per cent of the cases which he exam-



A



B

FIG 2—X-ray appearance six weeks after a gastrectomy using a small stoma. It will be noticed in (C) and (D) that there is barium in the proximal loop, this has been pushed back by the radiologist. (A) The barium is seen to run straight through the stoma and into the jejunum after taking the first swallow. (B) Some seconds later the stoma is seen to close and the stomach fills and distends. Note the size and the level of the air bubble.



C



D

FIG 2—(C) The stoma is open and the barium is seen flowing into the jejunum. Peristalsis is taking place in the stomach as shown by the size and the level of the air bubble. (D) The stoma is closed and the stomach is undergoing peristalsis.

med with the gastroscope Vitkin⁷ believed that out of a series of 132 cases with full length stoma all had a chronic jejunitis, with the exception of five patients where improvement was observed, it persisted in the remaining 127 cases for years. This is responsible for vague abdominal discomfort often not complained of but tolerated by many patients. In our series of 80 cases, followed up radiologically, only one had definite evidence of jejunitis.



FIG 3—Barium meal 20 hours after a gastrectomy using the small stoma and showing the barium passing into the jejunum. Note the position of the esophagus indicating the level of the resection and the size of the remnant before dilatation has occurred.

(d) Leakage at the duodenal stump may be due to faulty closure but we are of the same opinion as Alleson¹⁹ and Tintel²⁰ that the commonest cause is obstruction of the proximal loop at the site of anastomosis preventing the passage of the normal duodenal and pancreatic secretions (1500 cc daily). This obstruction may be caused either by kinking at the upper part of the anastomosis or by edema—producing a temporary paralysis of the proximal jejunum.

With a small stoma, the amount of edema is minimal and if the jejunum is stitched to the closed upper part of the gastric remnant, edema and kinking cannot occur at the same place. Slight kinking or edema in themselves may not

be sufficient to cause obstruction but when they occur together, complete obstruction may be precipitated (Fig 4)

In the 118 instances in which we have used a small stoma these points have been substantiated. There has been no case of leakage of the duodenal stump and in only nine cases has postoperative gastric suction been necessary.

Seven of these cases had slight postoperative hemorrhage. In one, there was an organic small bowel obstruction for which further operation was necessary on the fifth day, when a loop of small bowel adherent to the inside of the wound, was separated, after which convalescence was uneventful. In one case, the

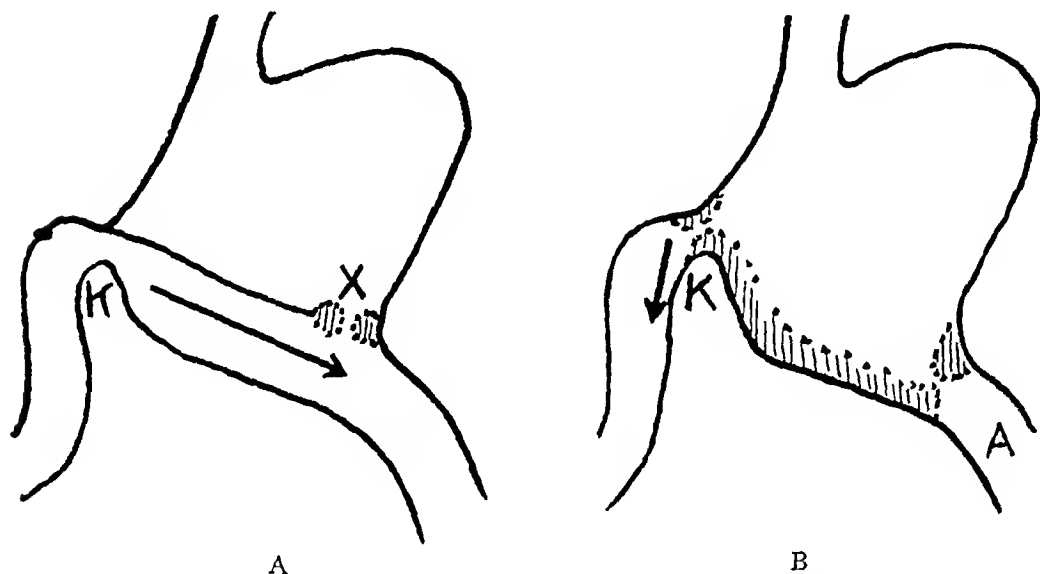


FIG 4—(A) Line drawing of a small stoma gastrectomy indicating the sites where edema (X) and kinking (K) may occur, but their positions are held apart.

(B) Line drawing of a large stoma gastrectomy indicating edema and kinking may occur at the same site.

stoma was made too small (1.5 cm). This also necessitated re-operation on the fifth day, with enlargement of the stoma. It is interesting to note that in this case the small gastric remnant had distended to 40 ozs. on the second post-operative day before suction was instituted, without any ill effects.

DUMPING

The dumping syndrome, as defined by Custer, Butt and Waugh²¹ of the Mayo Clinic, consists of four cardinal and almost invariable symptoms occurring 15–30 minutes after food.

They are

- (1) Profound nausea and weakness
- (2) Generalised unpleasant feeling of warmth
- (3) A cold sweat especially of the forehead and face
- (4) Palpitation

The cause of this syndrome is still debatable. There are three possibilities.

1 *Sudden distention of the jejunum* While sudden jejunal distention does cause a feeling of fullness immediately after food is swallowed and is exceedingly common after operations of the Polya wide stoma type, it cannot be regarded as the primary cause of dumping because when levulose is used in place of dextrose to distend the jejunum, the flushing, sweating and lassitude do not appear.

2 *Jejunitis* It has been observed that the majority of cases with the dumping syndrome show radiologic evidence of jejunitis but this may be in itself the result of too rapid emptying. In those cases in this series which have exhibited the syndrome, there has been no evidence of jejunitis.

3 *Hypoglycemia* It has been recognized for a considerable time that after gastrectomy or gastro-enterostomy, carbohydrates are more rapidly absorbed than usual.

This rapid absorption results in an over-stimulation of the production of insulin which in turn leads to a sudden drop of blood sugar level and results in hypoglycemia 1-1½ hours after food. Severe hypoglycemia may induce the excessive secretion of adrenalin which may simulate in every respect the dumping syndrome.

Since, however, the dumping symptoms usually occur within half an hour after food, it will be seen that there is some room for doubt as to the validity of this theory. It may be, however, that the rate of fall in blood sugar level from hyper- to hypoglycemia is associated with the upset.

The one constant feature which is present in all these theories is too rapid emptying of the stomach.

Gilbert and Dunlop¹⁶ reported that 35 per cent of patients who had had gastrectomy of various types carried out presented the dumping syndrome.

In this series, there have been 17 patients (15 per cent) from whom the history of the dumping syndrome could be elicited by asking leading questions. Twelve of these patients were symptom free within three months of operation. Of the remaining five, three have only had a three months' follow-up and are improving, in one case the syndrome has persisted for two years, and in one case for one year. Both of these, however, are able to work. We think these figures compare very favorably with those to be found in Gilbert and Dunlop's¹⁶ series in which 10 per cent of their gastrectomy patients were unfit for any form of employment because of the dumping syndrome.

It is interesting to note that a number of patients who presented themselves for operation had symptoms identical with the dumping syndrome preoperatively. All except the five already referred to have completely cleared up after operation. It has been found by Abrahamson²³ that patients suffering from duodenal ulcer have a low blood sugar level. This is an interesting observation which we hope to investigate further.

It is probable that the small incidence of persistent dumping in this series is due to the delayed emptying time of the gastric remnant due to the early development of a sphincteric-like action of the small stoma.

While many people believe that the size of the stoma has no influence on the emptying rate and that this is controlled only by the size of the lumen of the jejunum, this view is not borne out by our experience. Forty cases have had a follow-through barium series and the average time taken for the stomach to empty has been 58 minutes. That is the time taken for the fluid level in the stomach to disappear as opposed to 15–20 minutes in patients who have had a full length anastomosis performed.

This delayed emptying time is not due to any organic obstruction as during the first few days barium flows straight through into the jejunum and the

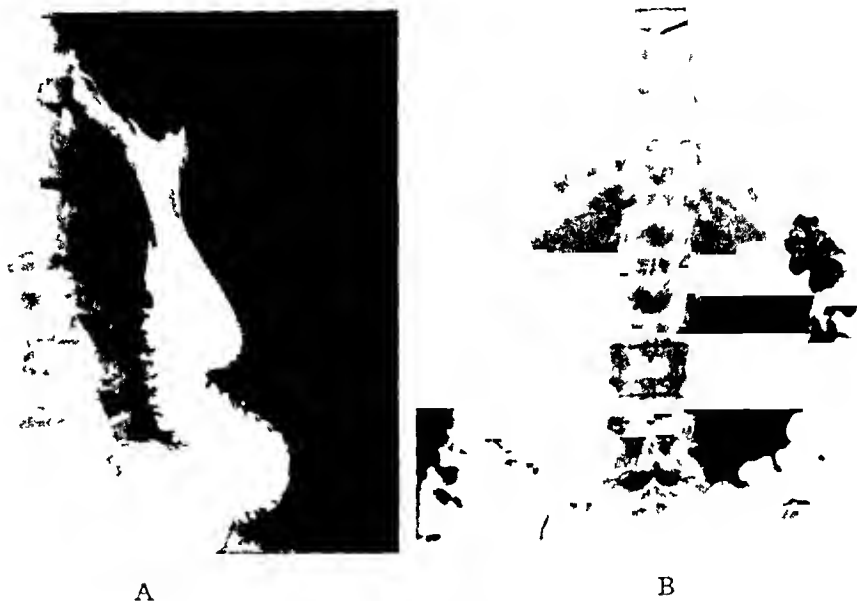


FIG 5—Barium meal 18 months after a Polya full length stoma gastrectomy (A) Immediately after meal showing very rapid emptying of the stomach and jejunal bulging (B) One hour after meal showing the stomach and small bowel completely empty

stomach empties rapidly. The majority, however, have developed delay and sphincteric-like action within six weeks.

In addition we have recently had a patient who had had a full length Polya type gastrectomy carried out 18 months previously with such severe postprandial dumping symptoms that it was necessary for her to lie down for one hour after every meal. She was also afraid to eat in a public place for fear of fainting. Accordingly a second operation was performed and the size of the stoma was reduced to $2\frac{1}{2}$ cms. The patient's symptoms were completely relieved by this operation and within 14 days she was able to take a full normal diet. A barium meal on the 11th day showed sphincteric-like action of the stoma and emptying time of over one hour (Fig 5). Three months later this patient had gained 10 lbs. in weight and appeared to be in perfect health.

Arguments against the use of the small stoma are as follows

(1) It may be said that regurgitation of alkaline juices into the gastric

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remnant with neutralization of any remaining free hydrochloric acid is prevented, but it is now generally accepted that if the resection has been adequate, stomal ulceration is exceedingly rare. In any case, most recurrent ulcers are jejunal and not gastric.

(2) Obstruction might occur later at the site of the stoma. We have followed some of these patients for over five years and we have had no single case of delayed postoperative vomiting or any evidence of late stenosis.

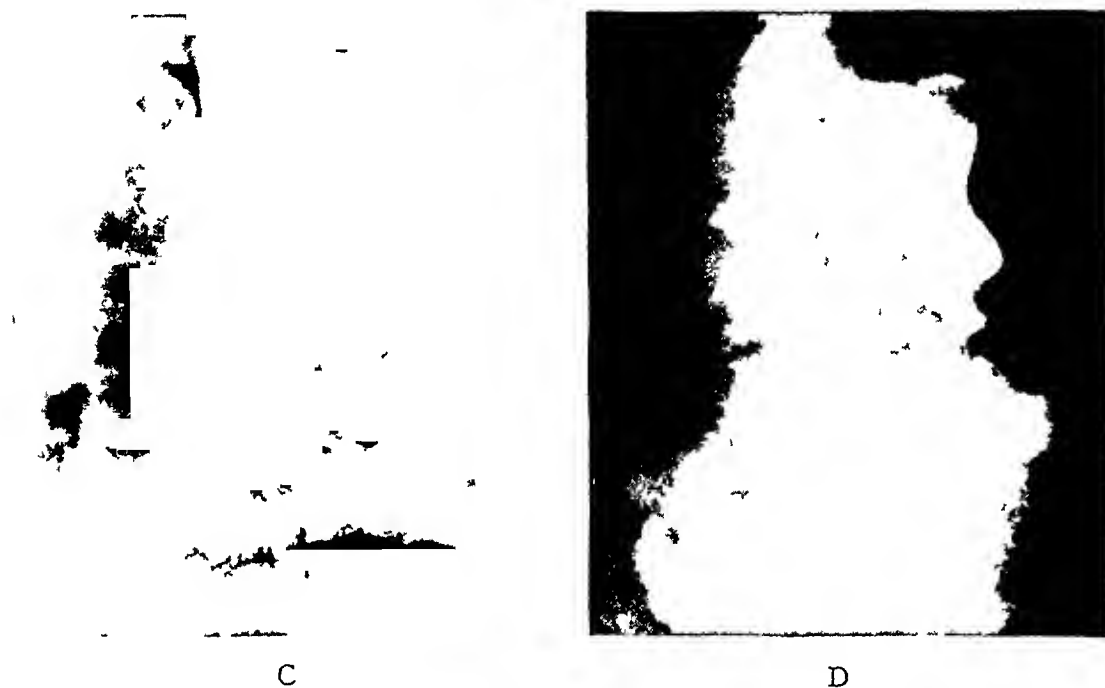


FIG 5—(C) Barium meal 11 days after a reconstructive operation on the stoma reducing its size to $2\frac{1}{2}$ cms. Lateral x-ray 5 minutes after the meal.

(D) One hour after the barium meal.

CONCLUSIONS

Evidence is produced from a series of 118 partial gastrectomies for peptic ulcer to show that a stoma of 2.5 cm. long has the following advantages:

- (1) The small stoma with a Hofmeister-Finsterer valve reduces the risk of incidence of—
 - (a) leakage at the duodenal stump
 - (b) leakage at the anastomosis
 - (c) postoperative hemorrhage from the anastomosis
 - (d) the necessity for routine postoperative suction
 - (e) jejunitis
- (2) The small stoma encourages—
 - (a) sphincteric action at the stoma
 - (b) delayed emptying time
 - (c) the ability to eat a full normal diet at an early date, shortening convalescence
- (3) The small stoma reduces the incidence of the dumping syndrome.

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THE OPERATIVE TREATMENT OF PECTUS EXCAVATUM*

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THE OPERATION FOR PECTUS excavatum was put in proper perspective by the detailed review of Ochsner and DeBakey¹ in 1939 and by the series of patients presented by Lincoln Brown² in the following year. Since the recent publications of Sweet³ and of Lester⁴ with their modifications of previous technics, pectus excavatum has been established even more firmly as a congenital deformity amenable to surgical correction.

Pectus excavatum (funnel breast, Trichterbrust) is a deformity of the thorax marked by a sharp posterior curve of the body of the sternum, deepest just before its junction with the xiphoid. The lower costal cartilages bend inward to form a depression, the lateral borders of which are angled more sharply than the superior and inferior portions. A paradoxical inward motion of the lower sternum is conspicuous on inspiration. The deformity is present at birth and usually is progressive. The chest becomes flat and thin, the dorsal spine kyphotic, the head thrust forward. In extreme instances the deepest portion of the concavity to one side of the midline may be posterior to the ventral surface of the vertebral bodies. In the undressed patient the concavity is conspicuous and unsightly and a source of embarrassment to young individuals of either sex. The deformity of rib cage and spine in the more severe instances is quite plain even when the patient is clothed. Physiologic disturbances may occur due to displacement of the heart or pressure upon it, but this is usually delayed until adolescence or later. There have been numerous reports of dyspnea and cardiac arrhythmias, such as paroxysmal tachycardia, their occurrence is not necessarily confined to the patients with the most severe deformities. It seems likely, however, that the dyspnea in the adult with shallow, rigid chest is on a pulmonary as well as a cardiac basis.

It is impossible to predict in which children the deformity will progress, since the mechanism of its production is still uncertain. The paradoxical depression of the sternum with each inspiration suggests that a short central tendon of the diaphragm might be responsible. Moreover, at operation one usually finds a tough fascial band tensely stretched between linea alba and sternum, the so-called substernal ligament. When this is divided the sternum may be elevated slightly without division of costal cartilages. On the other hand, the defect is generally obvious at birth and it seems unlikely that it has been produced solely by the pull of the diaphragm during fetal respiration.

It has been our feeling that operation should be undertaken in the more severe instances to correct the existing deformity and to prevent its progression. The younger the patient at the time of correction, the more favorable are

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his chances for attaining a normal appearance with subsequent growth of the thoracic cage

The indications for operation are (1) cosmetic, (2) orthopedic, and (3) physiologic

(1) The deformity itself is a source of concern to children and parents and a basis for teasing by playmates. The extent to which this has disturbed a

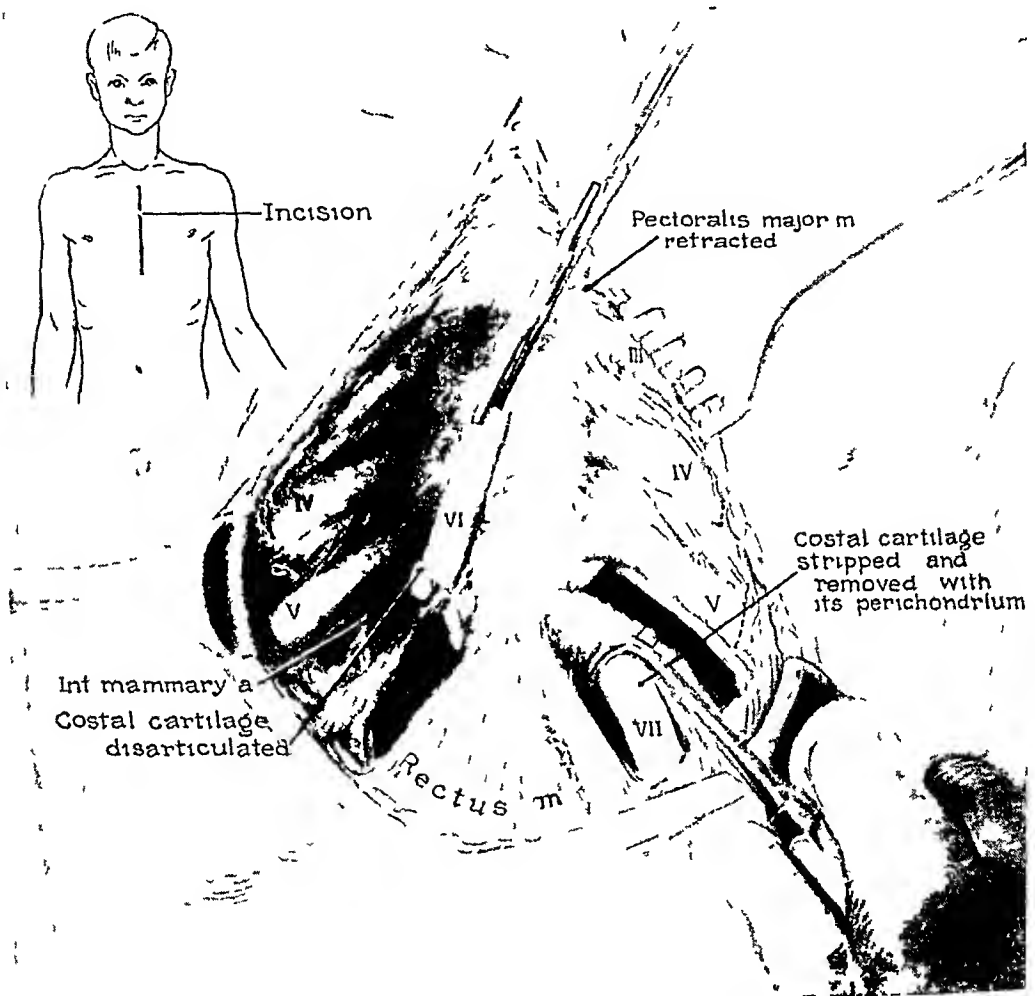


FIG 1—Midline incision from manubrium to epigastrium. The pectoral muscles are stripped back and the costal cartilages resected together with the perichondrium. The entire deformed segment of each involved cartilage is resected.

patient and his family is usually fully appreciated only after the operation. The correction of the defect seems to permit patient and family alike to discuss freely what had previously been minimized by a protective reticence.

(2) The antero-posterior flattening of the chest and the kyphosis will gradually disappear, if operation is performed early enough. As indicated hereafter, prophylaxis is better than cure.

(3) If dyspnea, exercise intolerance, or cardiac arrhythmias are present, operation is strongly indicated.

In children with pronounced defects, operation should be undertaken before there is any marked general thoracic deformity and before physiologic disturbances occur. One cannot predict which children will suffer most, if not operated upon. On the other hand, one may say that a less formidable operation in infancy will probably ensure normal development, whereas a more extensive operation some years later may secure only a partial correction of the deformity.

The procedure we have employed differs in some respects from those reported. It is designed to prevent any further deformity and to correct the existing deformity. For this reason we have felt it necessary to divide the xiphi-sternal articulation and substernal ligament and to resect all the deformed

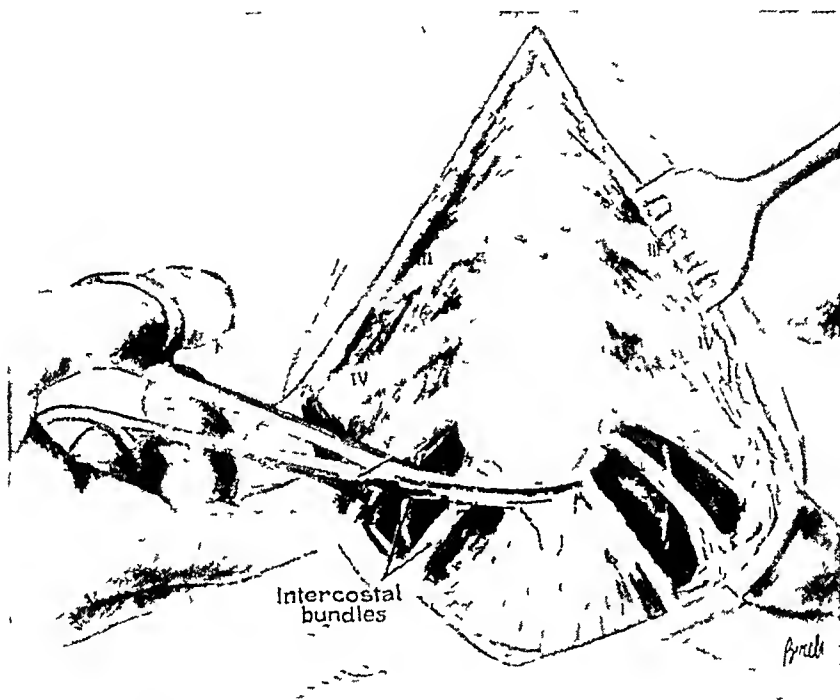


FIG 2—The two lowermost costal cartilages on each side have been resected, giving access to the xiphoid. The xiphi-sternal articulation is divided.

costal cartilages for the length of their deformity. The usual transverse cuneiform osteotomy is performed at the sterno-manubrial junction and the corrected position maintained by braided silk sutures. No traction apparatus is employed. The extensive defect resulting from excision of all of the deformed cartilage makes it impossible to suture the remaining cartilage ends to the sternum. No cast or other apparatus is employed to support the chest.

Technic. Under intratracheal ether anesthesia a midline incision is made from manubrium to epigastrium. The upward rise of the xiphoid and epigastrium from the sternal hollow is often nearly vertical and the sharp declivity makes it difficult to work in this area. In infants and small children it is relatively easy to strip the pectoral muscles from the sternum, exposing the costal cartilages. With the periosteal elevator all of the deformed cartilages are

exposed for the full extent of their deformity. The two lowermost cartilages on each side are divided at the lateral edge of the deformity and are then disarticulated from the sternum (Fig 1). In infants and children it is exceedingly difficult to perform subperichondral resection and no attempt is made to preserve the perichondrium. The deformity is such that the lowermost cartilages on each side usually lie together like the ribs of a fan, hindering exposure of the xiphoid. Only after these cartilages have been resected is one readily able to expose and separate the xiphisternal junction. As the scissors open the



FIG 3—Segments of costal cartilages removed at operation on Patient M. K., Case 2. The full length of the malformed portion of each involved cartilage is removed. This patient was four years old and notice that the lower segments are almost five centimeters in length.

xiphisternal joint (Fig 2), one can usually see the tough fibrous substernal ligament behind it. When this is divided the xiphoid pulls well away from the sternum—at times with an audible snap. Any remaining attachments of the rectus muscles to the sternum are divided. The finger can then be introduced into the mediastinum and the sternum freed of diaphragmatic attachments until the finger reaches freely to the manubrium. At this point one has completed what is essentially the “limited” operation of Brown. In one infant (Case No. 3) we had planned to do no more than this but found that there was still

a marked deformity and so continued the operation. The remainder of the deformed costal cartilages on both sides are then removed. The number varies with the severity of the deformity. We have taken from three to five cartilages on each side, resecting the full length of the deformed segment (Fig 3). The intercostal structures are divided so that the body of the sternum is free except for its junction with the manubrium. A transverse cuneiform osteotomy (Fig 4) is performed at the beginning of the downward curve in the sternum, cutting through to the posterior cortex. In the first two patients we employed an electric saw but now find osteotomes and an ordinary gouge to be simpler and more convenient. The sternum is then bent sharply anteriorly, fracturing

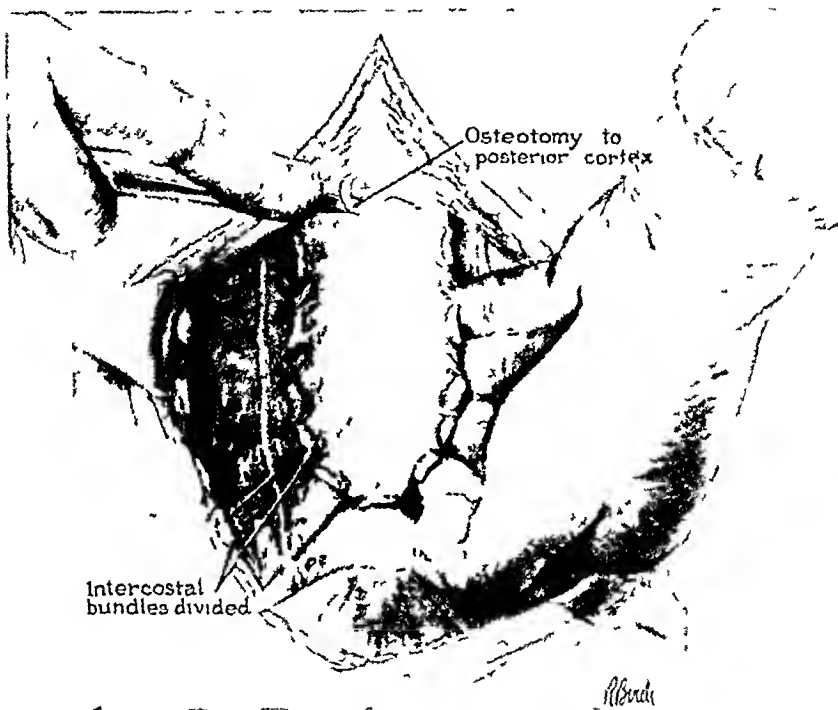


FIG 4—Five costal cartilages on each side have been resected and the corresponding intercostal bundles have been divided. The sternum is freed except at its upper end. With the gouge a transverse osteotomy is performed.

the posterior cortical lamella. Mattress sutures of braided silk are placed through the bone at the site of the osteotomy (Fig 5) to secure the two portions of the sternum in a slightly over-corrected position. These sutures are reinforced by 00 silk sutures placed in the periosteum. In the first two patients we used wires for external traction, but a fatal pyogenic infection in our second patient led us to abandon this technic, and we have seen no need to return to it. We have considered intramedullary fixation with a Kirschner wire, but in a recent adult patient with another type of sternal deformity, requiring two transverse osteotomies, sutures alone sufficed despite a heavy bony structure. Since the resected segments of cartilage are 3–5 cms. in length, we have considered it unwise to suture the remaining cartilage ends to the sternum. Despite this, the patients have not suffered from respiratory embarrassment. The

pectoral muscles are resutured (Fig 6) to the edges of the superior portion of the sternum. All patients have received prophylactic blood transfusions from the outset of the operation. Of eight children operated upon, seven convalesced rapidly and may be considered excellent results. One child immediately after operation developed high fever and a massive wound suppuration which presently eroded the pleura and produced a fatal empyema. This child had bronchiectasis (as in Lincoln Brown's first patient), but the infection was most probably due to some gross break in technic in the operating room.

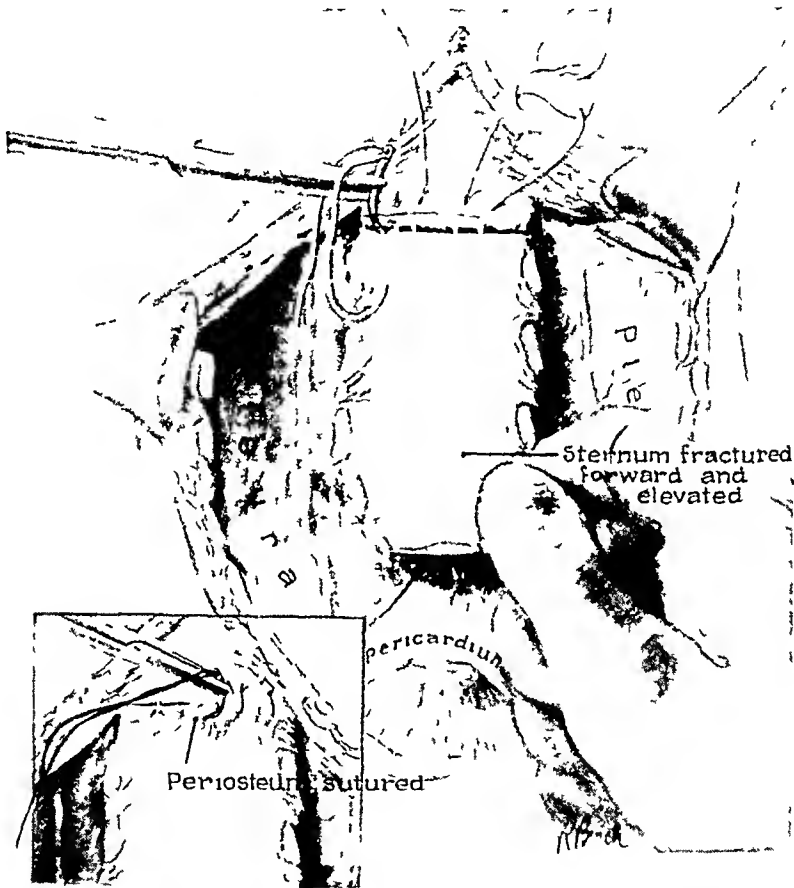


FIG 5—The sternum is elevated anteriorly, fracturing the posterior plate at the level of the osteotomy. The corrected position is maintained by mattress sutures of braided silk placed through the bone. The periosteum is then sutured with black silk.

CASE REPORTS

Case 1—R. K., 409665. This was a thin, undernourished boy of 10. He had been noted at birth to have a "caved-in chest." His father was said to have the same deformity. It was thought that the boy's deformity had been increasing in severity. He had always been a "mouth breather," but no other cardio-respiratory symptoms had been noted. There was a marked funnel chest with a moderate degree of paradoxical respiration. The defect was long and narrow. His posture was poor with a forward thrust of the neck and a rounded dorsal spine.

PECTUS EXCAVATUM

On January 15, 1947, the five lowermost costal cartilages on each side were resected. A transverse osteotomy was performed in the sternum and sutured with silver wire. Traction was maintained on the sternum by wire sutures attached to a plaster cast. In two days he was out of bed. The traction apparatus was removed on the 15th day. On the 20th day measurements with obstetrical calipers showed that on inspiration the sternum moved outward a half centimeter instead of retracting one centimeter as before operation. He was last seen October 4, 1948. The improvement has been maintained.

Case 2—M. K. A-51517 This was a boy 3 years and 9 months old who had been hospitalized repeatedly because of respiratory infections which had been diagnosed as pneumonia on several occasions. He had wheezed from birth. The sternal deformity was

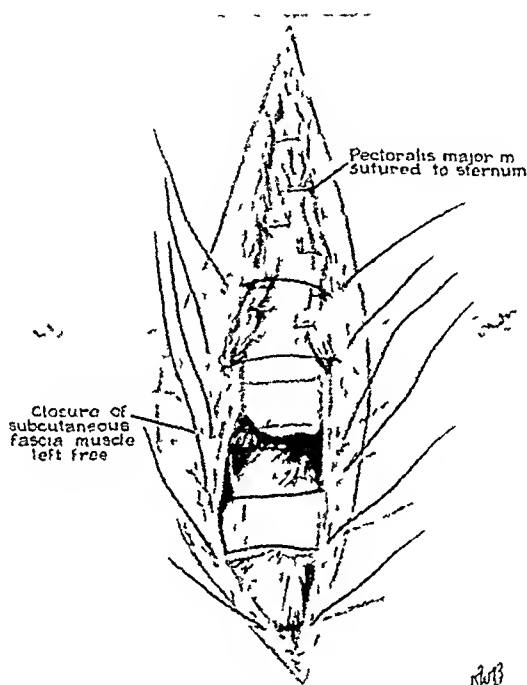


FIG 6—The pectoral muscles are sutured to the sternum in the upper portion. No attempt is made to replace the xiphoid or to re-attach the recti.

noted soon after birth. There was no family history of such a deformity. The child was malnourished and chronically ill. There was marked retraction of a deep sternal hollow and of the attached costal cartilages. He had a cough productive of whitish purulent sputum. There were rales everywhere over the lungs. Bronchograms showed bronchiectasis of the right lower lobe. It was decided that he would tolerate lobectomy better with increase in vital capacity resulting from correction of the pectus excavatum.

On January 21, 1947, the five lowermost costal cartilages on each side were resected from beyond the beginning of their curvature laterally to the sternum medially. The xiphoid was divided from the sternum and the substernal ligament divided. A wedge osteotomy was made with the electric saw and repaired with silver wire sutures, correcting the position of the sternum. Traction on the lower end of the sternum was made on a silver wire passing through the sternum and out through the skin, passing through a hole in a previously made plaster cast. On the third day after operation he developed a severe wound infection with hemolytic staphylococcus aureus. The wound broke down, empyema thoracis developed, and the child succumbed.



A



B

FIG 7—Case 3 B V, age 2 years (A) Before operation (B) Ten months after operation



A



B

FIG 8—Case 4—R E, age 7 years (A & B) AP and oblique views before operation

PECTUS EXCAVATUM



FIG 8—(C & D) Preoperative lateral roentgenograms in expiration and inspiration. Note the marked change in contour and the paradoxical inward movement of the sternum on inspiration. A stripe of thick barium paste applied to the midline demonstrates the sternal contour.

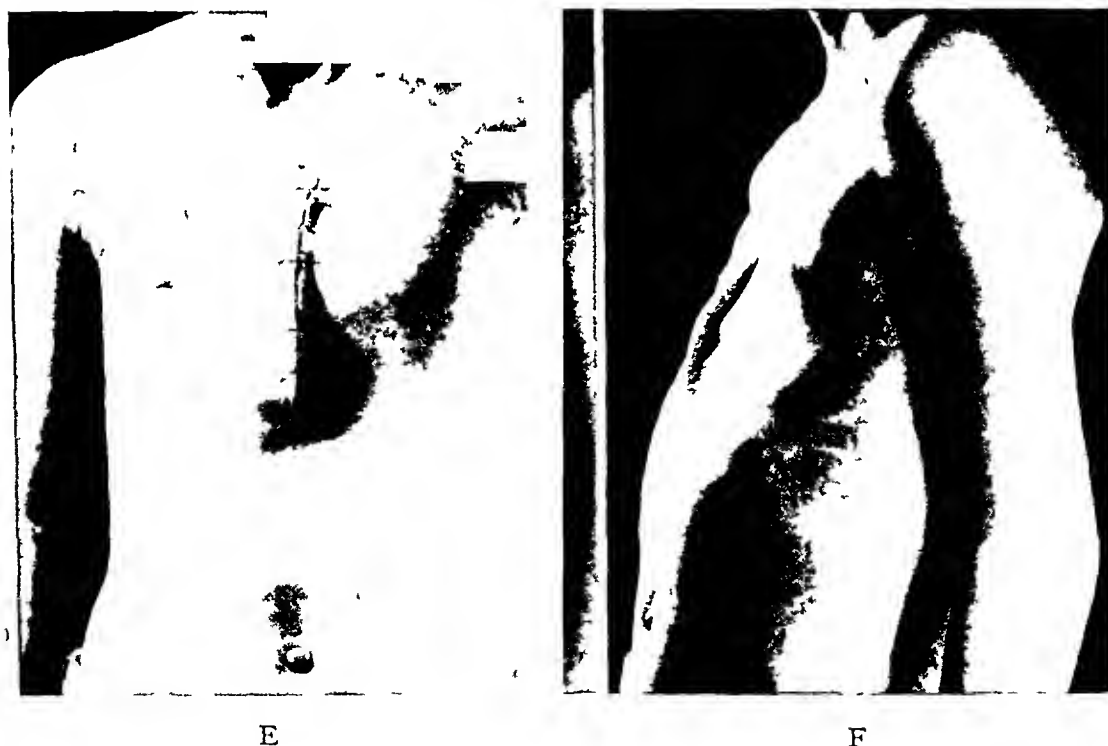


FIG 8—(E & F) AP and oblique views ten days after operation.

Case 3—E V, 420671 This was a 2-year-old boy whose development was retarded because of a birth injury. He had always been a "mouth breather" and had frequent upper respiratory infections. There was a deep round depression of his lower anterior chest which was thought to be increasing in severity (Fig 7a). There was no familial history of such a deformity. There was prominent paradoxical movement of the incurved portion of the sternum. The child was vigorous and well nourished.



G

FIG 8—(G) Postoperative roentgenogram. The sternum is straight. The ridged cutaneous closure elevates the barium stripe. Roentgenograms taken in deep inspiration show the sternum equally straight and flat.

On May 15, 1947, operation was performed. It had been planned to do the "limited" operation, but resection of 3-4 cm lengths of the 2 lowermost cartilages and separation of the xiphoid from the sternum with division of the substernal ligament failed to correct the deformity, although the paradoxical movement of the sternum ceased. Two more cartilages were, therefore, removed on each side. A transverse osteotomy was performed at the upper border of the defect, and the sternum was lifted anteriorly and held in place by a braided silk suture. He was sitting up and playing by the second day and was dis-

charged on the fourteenth day. Correction of the defect was satisfactory and has been maintained as seen in the photograph taken 10 months after operation (Fig 7b)

Case 4—R E, 450812 (Fig 8) This was a 7-year-old boy whose funnel chest was noted at birth. There was no familial history of such a defect. The boy was active and healthy, but was conscious of the defect which worried his parents and grandparents. The deformity was both wide and deep with pronounced paradoxical movement. There was no cardio-respiratory disability and the heart was not displaced.

At operation on February 12, 1948, long segments of the four lowermost costal cartilages were resected, the xiphisternal joint and substernal ligament were cut through, the sternum freed from the intercostal structures, and a transverse cuneiform osteotomy was performed superiorly. The sternum was fractured into proper alignment and maintained by braided silk sutures placed through the bone. This corrected the deformity completely, leaving a space of about 6 cms between the heart and the sternum which had pre-



FIG 9—Case 5 P S, age 3 years (A & B) AP and oblique views of child before operation

viously been almost in contact. The soft tissues were repaired as in the previous instances. He was out of bed on the fourth day and was discharged on the seventh day with a satisfactory correction. The paradoxical respiration was abolished and the hollow was corrected, but a downward tilt from the angle of Louis (Fig 8g) suggested that we might better have resected 5 costal cartilages on each side instead of 4.

Case 5—P S, 457408 (Fig 9) This 3-year-old girl had been known to have a "cavity in the front of her chest" from the time of birth. There were no other known instances of this deformity in the family. The child was first seen when she was two years old. The defect was marked. Operation was advised, but refused. A year later all observers were agreed that the defect was much more conspicuous, although asymptomatic. The excavation was a deep one, 6 cms broad with maximal depth just above the xiphoid. The heart seemed to be displaced to the left. There was classical paradoxical inspiratory accentuation of the defect.

On April 13, 1948, all of the deformed portions of the lower 5 costal cartilages were removed, the xiphisternal articulation and subcostal ligament were cut through, the sternum



C



D

FIG 9—(C & D) AP and oblique views of child taken a week after operation



E



F

FIG 9—(E) Preoperative roentgenogram. The barium outlines the hollow in the chest. The posterior surface of the sternum almost reaches the ventral surface of the vertebral bodies. (F) Postoperative roentgenogram. There has been a vast change.

PECTUS EXCAVATUM



FIG 10—Case 6 B P, age 5 years (A & B) Before operation Appearance at rest and on forced inspiration Note paradoxical displacement of sternum on inspiration (C & D) After operation Appearance at rest and on forced inspiration There is no paradoxical displacement of sternum and entire configuration of torso is much improved

was freed, and a transverse osteotomy was performed just distal to the angle of Louis. A single suture of braided silk held the sternum in the corrected position. Bilateral pleural perforations were recognized during the operation and treated at its conclusion by pleural

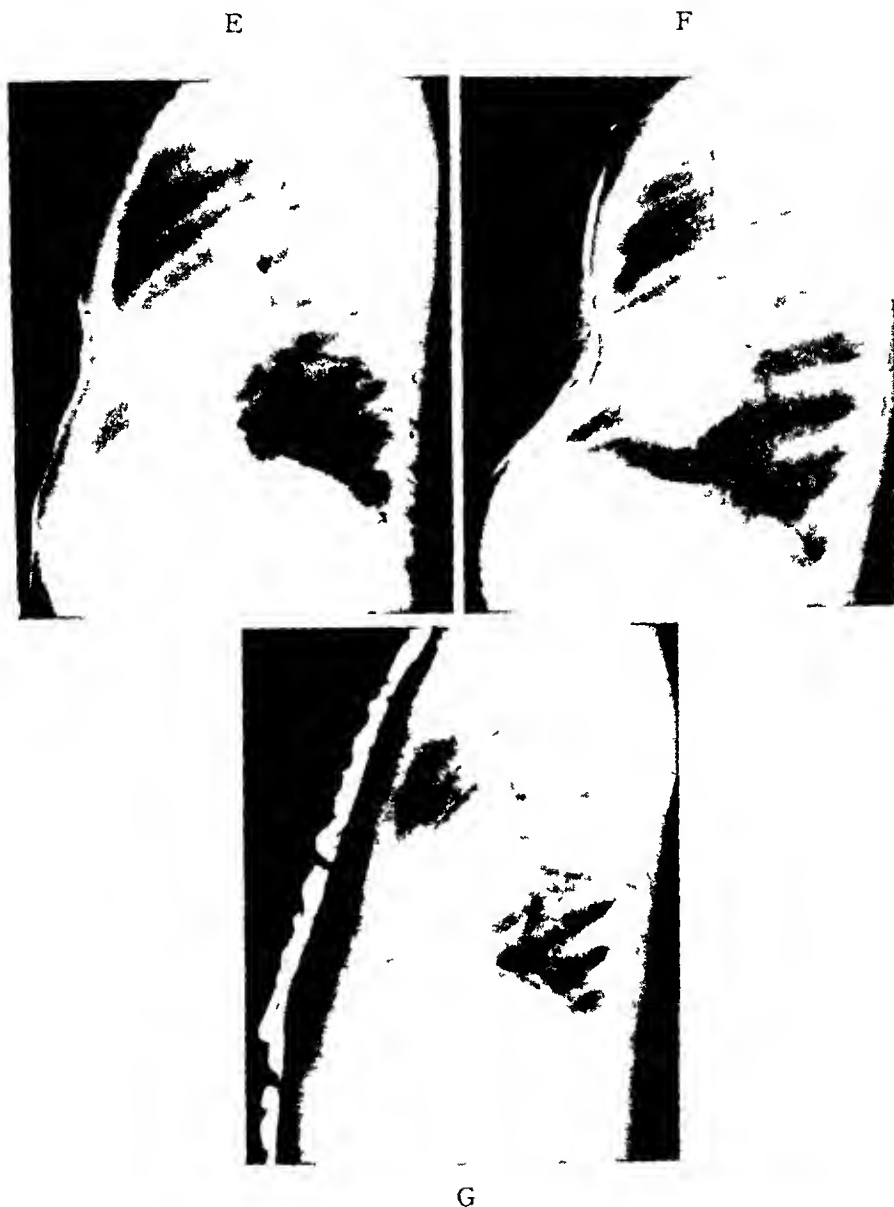


FIG 10—(E & F) Preoperative roentgenograms in expiration and inspiration. Paradoxical displacement of sternum is striking. (G) Postoperative roentgenogram. The barium stripe painted on the chest is deceptive. Close inspection shows that the sternum was fractured a little too low. Had five costal cartilages been removed on each side instead of three and the sternum then been fractured more cephalad, a more nearly perfect result would have been achieved.

aspiration. Except for a temperature of 100-101 degrees for the first 5 days, recovery was smooth and she left the hospital on the eleventh day with a good correction of her deformity by clinical and roentgenological examination.

PECTUS EXCAVATUM

Case 6—B P, 406240 (Fig 10) This 5-year-old girl had been noted from birth to have a depression of her lower sternum. At the age of 7 months she had an adenoidectomy for wheezing respirations and at 12 months radium was applied to lymphoid tissue in the nasopharynx. Thereafter there was no respiratory difficulty. The parents were certain that the deformity had progressively increased in severity. On physical examination she showed typical pectus excavatum of moderate degree. The depression was not as deep, nor was as much of the sternum involved, as in the other patients. Paradoxical movement of the sternum with inspiration was fairly pronounced.

On June 3, 1948, operative correction was performed. Only 3 costal cartilages on each side were removed. The xiphoid was disarticulated, the sternum isolated, and a transverse osteotomy performed. The sternum was maintained in the corrected position with braided silk sutures. Convalescence was rapid and easy. She was up walking on the following day and left the hospital on the eighth day. The result, by physical and roentgenologic examination, was good.

Case 7—R S, 465631 This was a boy of 22 months whose chest deformity had been noticed since birth. The parents remarked that it had been increasing progressively, although he seemed to be well and had no symptoms. Physical examination showed an attractive child with a pronounced sternal concavity, both deep and broad. Paradoxical movement was conspicuous. In the roentgenogram the heart appeared slightly displaced to the left.

On June 29, 1948, operative correction was performed. The 4 lowermost costal cartilages on both sides were removed for the length of their deformity. The xiphisternal articulation was divided. A transverse sternal osteotomy was performed just distal to the angle of Louis and the sternum fractured anteriorly and maintained in this position by heavy silk sutures. The pleura was entered on the left. During the procedure it was obvious that the left edge of the sternum and the two or three lowermost costal cartilages on the left had pressed against the heart. The child convalesced smoothly and was discharged on the eighth postoperative day with a satisfactory correction.

Case 8—C L, 466265 This girl of 7 years had been born with a depressed sternum and her pediatrician referred her for operation because of increase in the degree of deformity. Her posture was poor and her exercise tolerance not equal to that of friends of the same age. Physical examination showed a child with a chest shallow in the antero-posterior diameter and with a conspicuous funnel deformity. The deformity was asymmetrical, being sharper and more acute on the right side than on the left. Paradoxical movement of the sternum was particularly prominent.

Operation was performed on August 3, 1948. Four costal cartilages were removed on each side, the sternum being treated in the usual fashion. She was out of bed and playing on the next day and left the hospital on the sixth day after operation. On the previous day 30 cc of serosanguinous fluid was aspirated from the wound. The correction of the deformity was complete and in three weeks the chest wall felt solid.

SUMMARY

Pectus excavatum is a progressive deformity of the sternum and costal cartilages which may be satisfactorily corrected by operation. The younger the patient, the greater is the likelihood of attaining a completely normal thoracic contour. Operation is indicated for removal of a cosmetic defect which is a social handicap, for correction of a skeletal deformity, and for alleviation of cardiac or pulmonary symptoms. Early operation is important as a prophylaxis against progression of symptoms and signs.

The deformed portions of all the involved costal cartilages on both sides are resected. The xiphisternal articulation and the substernal ligament are divided and the body of the sternum isolated except for its attachment to the manubrium. A transverse osteotomy at the superior border of the defect permits the sternum to be elevated into the corrected position which is maintained by braided silk sutures in the bone. No external traction is employed and no type of cast or other support is required.

We have treated eight children ranging in age from 22 months to 10 years. In seven there were no complications and the results were excellent. One child died of a fulminating wound infection.

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THE TREATMENT OF ACUTE ANURIA*†

WITH EVALUATION OF PERITONEAL LAVAGE

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ACUTE ANURIA due to potentially reversible lesions, resulting from a variety of causes, *ie*, transfusion reaction, crush syndrome, sulfonamides, bichloride of mercury poisoning, shock, etc, but which are essentially similar in their histopathology, presents a therapeutic challenge to the clinician to prolong life until renal healing may occur

Various procedures for possible alleviation of renal shutdown, such as intravenous procaine, spinal anesthesia or splanchnic block, or methods for reducing azotemia and prolonging life to the period of reversibility, such as peritoneal lavage^{1, 2, 3, 4, 5, 6, 7, 8, 9} or the artificial kidney^{10, 11} have been advocated in recent years. Several of the procedures are old^{12, 13, 14, 15} but had not been adapted to clinical use until the work of Fine *et al*^{2, 3, 9}

This paper presents our experiences in the treatment of acute anuria in six patients with potentially reversible tubular lesions, and in one patient with acute glomerulonephritis. Four of our patients died and three lived

DEFINITIONS

A 24-hour urinary output of 50 cc or less was considered as anuria, between 50 and 100 cc as oliguria

METHODS

The technique of peritoneal lavage used in all but Case I (W H) was as follows. Under local anesthesia the inlet tube, a dePezzar catheter, was placed in the upper abdomen and the outlet tube, a Chaffin tube,¹⁶ was guided into the pelvis by a uterine sound (Fig 1). One of the limbs of the Chaffin tube was connected with an adequate length of rubber tubing and drainage accomplished by gravity, and the other limb was clamped off. Or, if mild continuous suction was applied to the first limb of the tube, the other limb was covered with sterile gauze and functioned as an air vent. The limbs were interchangeable. The wounds around each tube were closed snugly in layers with interrupted sutures, and the skin edges sealed with collodion-cotton.

Irrigating fluid was run in at the rate of approximately one liter every 45 minutes. The composition of the fluids we used compared with the solution used by Fine *et al*² is shown in Table I

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TABLE I—*Composition of Lavage Fluids*

	*Modified Ringer s Lactate	*Modified Tyrode s	Modified Tyrode s (Fine et al)
	Gm /liter	Gm /liter	Gm /liter
Sodium lactate	3 0	3 0	
Sodium chloride	6 0	6 0	8 0
Potassium chloride	0 4	0 2	0 2
Calcium chloride	0 2	0 2	0 1
Magnesium chloride		0 1	0 1
Sodium acid phosphate			0 05
Sodium bicarbonate			1 0
Glucose	20 0	20 0	20 0
Added to each liter			
Penicillin	20 000 units	20 000 units	2500-5000 units
Heparin	2-5 mg	2-5 mg	0 25-0 5 mg

* Los Angeles County Hospital

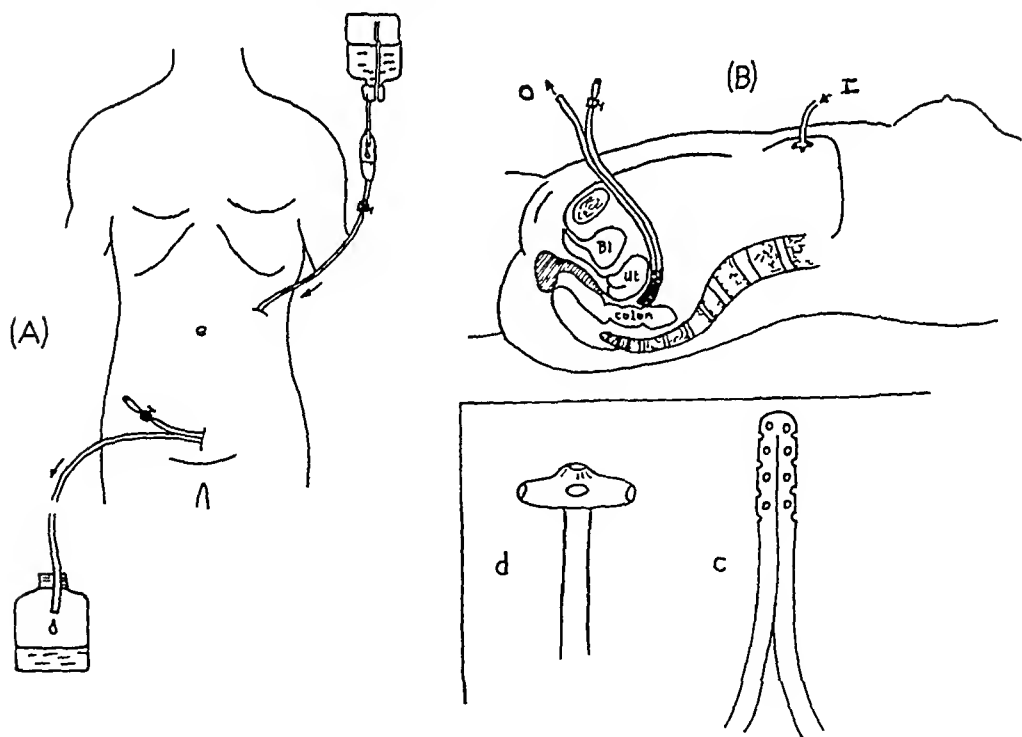


FIG 1—Diagram of peritoneal lavage (A) Front view of abdomen with tubes in place (B) Side view I Inlet—dePezzar catheter (d) O Outlet—Chaffin tube (c)

The blood non-protein-nitrogen, chloride, carbon-dioxide combining power and sugar were determined daily. In addition, in several cases, a detailed electrolyte balance study was made on the serum and peritoneal-outflow-fluid, with daily determinations of the cations—sodium, potassium, calcium and magnesium—and the anions—chloride, bicarbonate and phosphorus. Blood pH, serum albumin and globulin and hematocrit levels were also determined. Serial electrocardiograms were taken on the majority of the patients. All chemical determinations were made by standard methods.

CASE SUMMARIES* WITH COMMENT ON THERAPY USED

Case 1—W. H.—White male, age 32, (L. A. C. H. No. 974-738), was admitted to the hospital because of a suicidal attempt with tincture of iodine. There was a rapid development of methemoglobinemia, methemoglobinuria and acute anuria. Inadequate peritoneal lavage was performed from the 6th to the 9th hospital day, with retention of irrigating fluid due to plugging of the outflow tube. He received between 2000 and 3000 cc of fluid intravenously daily during the first 5 days and later between 1000 and 2000 cc daily. One-half to two-thirds of the total intravenous fluid contained sodium. Death occurred on the 9th hospital day.

Autopsy revealed acute pulmonary edema. There were a few strands of fibrin in the peritoneal cavity. The kidneys showed evidence of massive intravascular hemolysis, with one-half of the nephrons filled with hemoglobin casts. The microscopic diagnosis was obstructive and necrotizing lower nephron (tubular) nephrosis (Fig. 2-A).

COMMENT

This patient was overhydrated. He received too much intravenous fluid containing sodium. Also, absorption of irrigating fluid from the peritoneal cavity was facilitated by blockage of the outflow tube and the simultaneous intravenous administration of a hypertonic solution (10 per cent glucose).

Case 2—R. O'N.—White male, age 21, (L. A. C. H. No. 1003-196), entered the hospital with a history of chills, fever, cough and chest pain of 10 days' duration which had been treated at home with an unknown amount of sulfathiazole and penicillin. On entry a diagnosis of pneumonia was made, and large amounts of penicillin were given. Despite this therapy he did poorly, developed a generalized edema, and progressive azotemia, with a good urinary volume. He received between 1500 and 2000 cc of intravenous fluid daily. The urine was loaded with pus, bacteria (*E. coli* and *gamma streptococcus*), and occasionally contained 15-20 red blood cells per high-power-field. A clinical diagnosis of sulfonamide nephrosis was made and peritoneal lavage was performed from the 16th to the 22nd hospital day, with clearance of 14-24 Gm of non-protein-nitrogen per day. Death occurred on the 22nd hospital day.

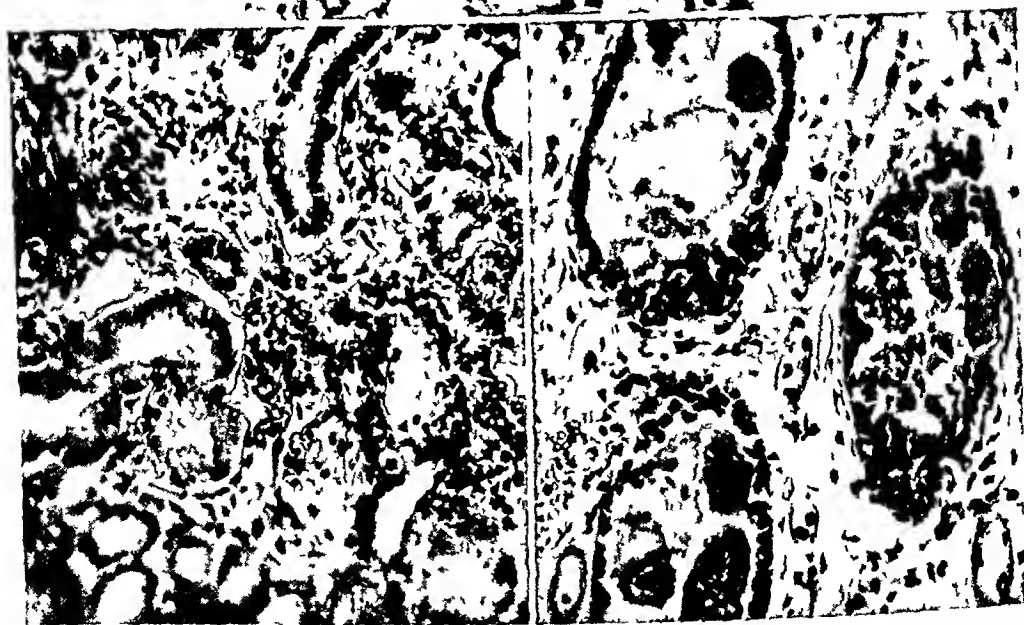
Autopsy revealed bilateral hydrothorax and pulmonary edema. There was an acute bacterial endocarditis. The renal lesion was an acute glomerulonephritis.

COMMENT

The correct diagnosis was not made in this patient. Since the majority of patients with acute glomerulonephritis survive the initial attack, it is questionable whether they should be candidates for peritoneal lavage. The lavage

* Drs. George Pearson, Raymond Bangle and Roy Byrnes assisted in the medical care and collection of laboratory material in several of the patients studied. Dr. Hugh Edmondson reviewed all the microscopic sections.

A



B

C

FIG 2—Photomicrographs of kidneys (A) (Case 1, W H—Iodine poisoning)—Obstructing and necrotizing lower nephron (tubular) nephrosis (B) (Case 3, H N—Transfusion reaction)—Healing lower nephron nephrosis (C) (Case 4, M G—Bichloride poisoning)—Necrotizing upper nephron nephrosis with moderate regeneration and internal hydronephrosis (See text for details)

worked well in clearing nitrogenous waste products, but the patient died of pulmonary edema. This patient likewise received too much intravenous fluid.

Case 3—H N—White woman, age 66, (L A C H No 1002-896), entered the hospital for a resection of a carcinoma of the rectum. She had a transfusion reaction on the 22nd hospital day while being prepared for surgery. Oliguria and progressive azotemia developed. Peritoneal lavage was started 6 days after the transfusion reaction, and was continued for 11 days with marked improvement in the azotemia. She received between 1000 and 1500 cc of intravenous fluid daily. Five days after the lavage was started generalized edema developed. This persisted and the patient died of pulmonary edema 19 days after the transfusion reaction. The 24-hour urine volume had reached normal levels 2 days before death.

Autopsy revealed severe pulmonary edema, an early bronchopneumonia, interstitial myocarditis, and a grade 3 squamous cell carcinoma of the rectum. The kidneys showed a healing lower nephron nephrosis with severe interstitial pyelonephritis (Fig 2-B).

COMMENT

This patient began putting out urine before her death, and it is noteworthy that the microscopic sections of her kidneys showed advanced healing of the tubular lesion. The use of a retention catheter was probably the cause of the ascending pyelonephritis. She received entirely too much intravenous fluid, a good share of which was hypertonic, and her circulation was overloaded. It is probable that cardiac failure due to the interstitial myocarditis was also a contributing factor in her edema and death.

Case 4—M G—White woman, age 32, (L A C H No 1009-649) entered the hospital because of ingestion of bichloride of mercury in a suicidal attempt. BAL was started within 6 hours of taking the bichloride of mercury and a full therapeutic course was given. Severe oliguria developed early and persisted for 21 days until her death. Peritoneal lavage was started on the 6th hospital day and was used continuously for 9 days. It was stopped for several days because of the development of peritonitis, but with the subsidence of peritoneal irritation, intermittent lavage was re-instituted later. There was effective clearing of nitrogenous waste products by this procedure. Intravenous fluids (isotonic) were restricted to 1000 cc per day except during the last few days of life when she received additional concentrated plasma and concentrated human albumin. She died on the 22nd hospital day of pulmonary edema.

Autopsy showed bilateral hydrothorax (minimal) and marked pulmonary edema. The kidneys showed a necrotizing upper nephron nephrosis, with moderate regeneration, and a marked internal hydronephrosis secondary to blockage of the collecting tubules by great numbers of casts, some of which were replicas of dead epithelium from the upper nephron (Fig 2-C).

COMMENT

This patient received too much intravenous fluid, especially in the last seven days of her life. It is doubtful if she ever could have put out urine through the blocked collecting tubules, but the immediate cause of her death, as in the others, was acute pulmonary edema. In addition to the intravenous fluid, she undoubtedly absorbed fluid from the peritoneum, especially during the time she received concentrated plasma, and concentrated human albumin intravenously.

Case 5—B B—Negro female, age 30, (L A C H No 974-738) Prior to entry to the hospital, this woman had a septic abortion and was anuric at the time of hospitalization (The exact cause of the renal suppression was never established) She received between 2000 to 3000 cc of intravenous fluid daily during the first 5 days (of which 1000 cc was normal saline) and developed generalized edema Restriction of fluid and sodium was begun on the 6th hospital day, and peritoneal lavage was performed from the 6th to the 10th day with good clearance of nitrogenous waste products On the 9th hospital day, her urinary output was 460 cc with gradual increase in volume thereafter The specific gravity of the urine remained at 1.010 for 82 days

COMMENT

This patient began putting out urine on the 9th hospital day She probably would have gotten well without peritoneal lavage Her spontaneous recovery thus was not jeopardized by overtreatment

Case 6—"X"—White woman, age 32 (outside hospital) This patient had a Porro Cesarean section and a day later was re-operated on for an actively bleeding cervical stump vessel She was transfused several times and was believed to have had a transfusion reaction Following this, she became severely oliguric and developed progressive azotemia She received on successive days 3800, 1700, 1250, 500, 1000, 700, 1150 cc of intravenous fluid On the 8th hospital day she developed marked generalized edema and a pericardial friction rub Peritoneal lavage was performed for 24 hours starting on the 9th hospital day Intravenous fluids were discontinued immediately preceding the institution of lavage and the oral intake limited to an occasional sip of tap water During the next 3 days generalized muscular twitchings developed She showed definite improvement on the 12th hospital day and was able to take a modified soft diet The 24-hour urine volume was normal by the 14th day, but the specific gravity remained at 1.010 for nearly 3 weeks

COMMENT

It is quite likely that this patient would have improved without peritoneal lavage since this was continued for only one day It did bring the blood non-protein-nitrogen down temporarily, and clinically she appeared more alert following its use She had a moderately severe generalized edema which disappeared rapidly with the restriction of fluids and sodium The elimination of intravenous fluids and sodium ions probably saved this patient from overhydration and death from pulmonary edema

Case 7—W O'Q—White male, age 37, (L A C H No 1004-828) attempted suicide with bichloride of mercury BAL was started within 2½ hours of the bichloride ingestion The patient became anuric within 6 hours After the 5th hospital day intravenous fluids were discontinued and oral fluids were restricted to 500 to 800 cc daily Gastric lavage was performed for 2 days with clearance of approximately 33 Gm of non-protein-nitrogen per day The 24-hour urine volume reached a normal level by the 9th hospital day The specific gravity remained low for 6 weeks

COMMENT

The only intravenous fluid administered to this patient after the 3rd hospital day was procaine 1 Gm in 250 cc of 2½ per cent glucose in water, repeated 3 times at 12-hour intervals He is the only patient in our series who never developed any edema In spite of a strictly limited oral fluid intake (500-800 cc per day) he had a diuresis after the 9th day He probably would

ACUTE ANURIA

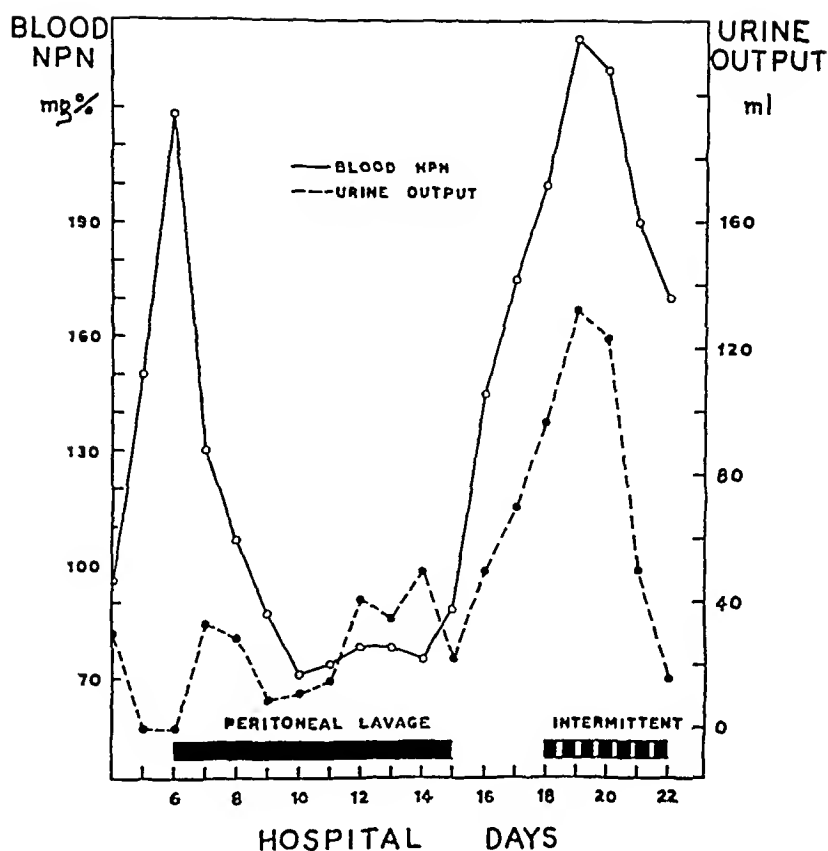


FIG 3 —(Case 4, M G—Bichloride poisoning) Results of peritoneal lavage on blood non-protein-nitrogen level

TABLE II—Adequate Urine Volume in Lower Nephron Nephrosis*

Hospital Day	Urine Volume in cc. (1)	Blood NPN mg %	Blood Sugar mg %	CO ₂ C P Vols %	Comment
1	over 1300	75	1300	13	Shock
2	over 1700	59	362	26	Cold right leg
3	over 2300	45			
4	over 1300				Sulfadiazine started
5	over 600				for <i>E. coli</i> sepsis
6	over 1000				
7	over 1000				
8	over 1000		148	57	
9	1300				
10	over 1100				
11	over 2200	174			
12	3000				
13	825	175			
14	1200	176			
15	1400				
16	2100	205	185	40	
17	1750				
18	1250	215			
19					Death

* History not discussed in paper as patient treated prior to present series 56-year-old Negro male entered in severe diabetic acidosis and shock. *E. coli* sepsis. Circulatory failure and gangrene of right leg (packed in ice). Autopsy showed lower nephron nephrosis due to shock and sulfonamides.

(1) Some of urine discarded without measuring, the amount recorded actually measured.

have recovered even if nothing (except BAL) had been done for him, but at least his recovery was not complicated by injudicious overhydration and sodium ion administration

DISCUSSION

Many case reports have demonstrated that peritoneal lavage^{1, 2, 3, 4, 5, 6, 7, 8, 9} is an effective means of removing nitrogenous waste products. The results in the six of our patients who had peritoneal lavage confirm this and are illustrated in Fig 3 (Case 4—M G) which shows a drop in the blood non-protein-nitrogen from 218 to 71 mg per cent with 4 days of peritoneal lavage (hospital days 6 through 9)

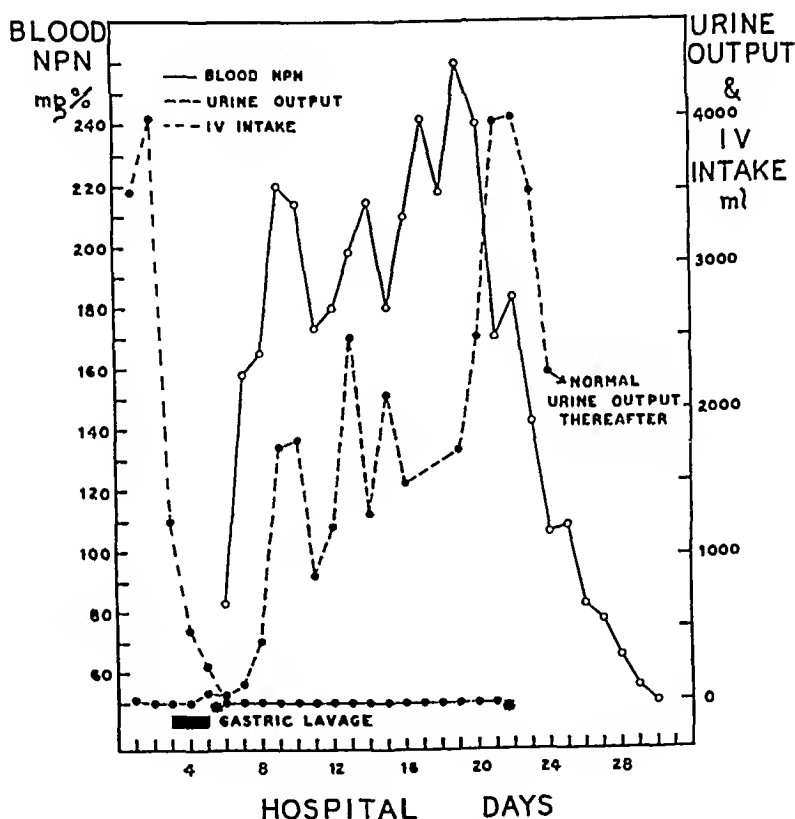


FIG 4—(Case 7, W O'Q—Bichloride poisoning) Intake, output and blood non-protein-nitrogen level

* No intravenous fluids between hospital day 5 and 21, oral intake under 800 cc per 24 hours

The characteristic microscopic pathology found in these acute lesions of either the upper or lower nephron are well illustrated in Fig 2 and require no comment due to the thorough description of Mallory¹⁷ and others¹⁸. Certain points, however, have previously received little or insufficient emphasis. Some patients with acute tubular lesions may have no anuria or oliguria. In spite of tubular damage they may have an adequate 24 hour urine volume. This urine has a low specific gravity and presumably comes from only a few functioning nephrons. Progressive azotemia does develop, however, just as when

anuria or oliguria is present. This is illustrated in Table II (lower nephron nephrosis due to shock and sulfonamide injury) which shows a 24 hour urine volume usually over 1 liter, with a blood non-protein-nitrogen which steadily rose from 45 to 215 mg per cent before death. Other patients may have several days of oliguria, and then put out an adequate 24 hour urine volume, but the blood non-protein-nitrogen level continues to rise since only a few nephrons are functioning. Fig 4 (Case 7—W O'Q, upper nephron nephrosis due to bichloride of mercury poisoning) shows a blood non-protein-nitrogen which rose from 158 to 260 mg per cent, with 24 hour urine volumes between 800 and 3800 cc from the 8th day to the 20th day. The fact that spontaneous diuresis will occur even with marked restriction of fluids is also seen in Figure 4. This patient had marked restriction of fluid intake after the 3rd day of anuria, but had a spontaneous increase in the 24 hour urine volumes from 125 cc to 1750 cc between the 7th and 9th days.

The problem of fluid and sodium retention has not been stressed sufficiently except by a few^{19, 20, 21, 22}. All of the patients in our series (except one, Case 7) were edematous at the time we were first consulted about their anuria. The importance of this problem is seen in the fact that the immediate cause of death in the four patients who died was severe pulmonary edema. The only patient who did not develop edema at any stage received only a small volume of intravenous fluid on the 3rd and 4th hospital days, and none from the 5th to the 21st hospital day (Figure 4).

It is obvious that with loss of the excretory function of the kidneys, in particular tubular function, the main control of extracellular sodium is lost. If any sodium is given it will be retained,²³ and will hold water with it. Barring severe loss of intestinal fluids (continuous nasogastric suction, diarrhea, etc.) there should be little loss of extracellular sodium and consequently little if any replenishment should be required. If acidosis of severe degree develops administration of a small amount of sodium may be necessary. This is preferably given orally in small doses (40 Gm of sodium bicarbonate) and repeated until the acidosis is moderately improved.

There is no evidence that alkalinization following a transfusion reaction or sulfonamide injury reverses the damage already done. Forcing fluids in anuria does not raise the glomerular filtration pressure or break "the tubular block," but merely increases the circulating blood volume²⁴ due presumably to diffusion of the glomerular filtrate into the peritubular capillaries.

Another reason for rigid restriction of intravenous fluids and sodium is based on the fact that patients late in the course of anuria tend to develop pulmonary edema spontaneously. This is presumed to be due to some ill-defined toxic effect of retention products on the alveolar capillaries.

With the onset of diuresis, in the recovery phase, the management as to fluids and electrolytes may vary from the above plan. Rapid and perhaps fatal loss of electrolytes may occur at this time. Sodium loss if present and indicated by acidosis or measurement of blood and urine sodium levels should be corrected by adequate replacement.

TABLE III—M G No 1009-649 Case 4

	DAY 4		DAY 5		DAY 6		DAY 7		DAY 8		DAY 9		DAY 10		DAY 11		DAY 12		DAY 13	
	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent
Cations	127		122		132	113	130		123		144	132	142	132	149	129	143	130	159	137
Na mEq	3 2		3 4		3 7	3 6	4 0	3 1	2 8		3 7	2 8	3 6	3 2	3 9	2 9	3 6	2 9	3 6	4 0
K mEq	4 4		4 4		4 3	3 1	4 8	3 3	3 5		5 2	3 8	5 8	3 8	5 8	3 7	5 9	3 8	5 8	3 8
Ca mEq	2 4		2 6		2 5	0 7	1 7	1 0	1 3		1 8	1 3	1 9	1 2	1 7	1 3	2 2	1 4	2 1	0 9
Mg mEq																				
Anions																				
HCO ₃ mEq	14		7		14		9		16		18		23		19		24		27	
Cl* mEq	72		72		76		91		82		79		77		77		83		84	
HPO ₄ mEq	4 0		5 7		5 2	1 4	3 2	1 3	0 8		2 6	0 6	2 2	0 8	3 1	1 0	2 7	1 0	2 3	0 8
pH	7 40		7 41		7 24		7 38		7 50		7 50		7 48		7 50		7 58		7 56	
Hematocrit %	33		33		31		31		30		30		31		29		25		22	
NPN* mg %	150		150		218	110	130	105	75		87	50	71	50	73	59	78	43	78	40
Creatinine* mg %																				
mg %	6 8		8 4		10 0	7 0	7 2		6 0		7 1	6 0	6 0	6 1	5 5	4 0	4 8	4 1	3 2	3 2
Albumin Gm %	4 0		4 3		3 6		4 0		4 1		4 0		4 1		3 8		4 1		3 9	
Globulin Gm %	2 3		2 6		2 0		2 1		2 3		2 4		2 7		2 6		2 9		3 0	
Total Protein Gm %																				
Sugar* mg %	6 3		6 9		5 6		6 1		6 4		6 4		6 8		6 4		7 0		6 9	
*Whole blood	123		117		190	1000	173	820	198		203	784	214	708	190	1152	178	1314	147	1070
	DAY 14		DAY 15		DAY 16		DAY 17		DAY 18		DAY 19		DAY 20		DAY 21		DAY 22		DAY 22a	
	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent	Serum	Pent
Cations	142	132	142		144		146		142	129	139	121	139	130		134		130	139	
Na mEq	4 5	4 3	5 4	4 1	6 6		7 0		7 4	4 4	6 4	2 6	7 1	3 6		6 3		3 3		
K mEq	5 5	3 7	5 3	3 6	5 0		4 9		4 5	3 6	4 4	4 0	4 2	3 8		4 4		4 6		
Ca mEq	1 8	0 7	1 7	1 2	2 0		2 3		2 5	1 4	2 3	1 3	2 2	1 4		2 1		2 1		
Mg mEq																				
Anions																				
HCO ₃ mEq	25		22		23		22		18		18		19		20					
Cl* mEq	71		79	107	70		70		68	48	82	109	81	97		79		100	83	
HPO ₄ mEq	2 2	0 8	2 3	1 2	3 2		3 8		4 9	1 9	5 1	0 0	4 2	0 7		3 1		2 5	0 6	3 4
pH	7 56				7 50				7 46											
Hematocrit %	27				31		31		29		28		25		24					
NPN* mg %	75	56	88	59	145		175		200	131	238	11	230	30	190	135	170	70	150	
Creatinine* mg %																				
mg %	4 1	4 2	4 9	5 9	9 0		9 5		13 0	7 9	10 3	1 2	8 9	5 5	7 3	6 7		3 8	5 5	
Albumin Gm %	3 4		3 2		3 4		3 5		3 7		3 4		3 3		3 0		3 1		3 2	
Globulin Gm %	2 8		2 8		3 0		2 9		3 0		2 7		2 5		2 2		2 4		2 5	
Total Protein Gm %																				
Sugar* mg %	6 2		6 0		6 4		6 4		6 7		6 1		5 8		5 2		5 5		5 7	
*Whole blood	128	885	155	816	103		110		134	1372	268	1700	138	1500	178		138	1860	193	
† Eight hour period																				

The treatment of shock and anuria when they co-exist is a more difficult problem. Initially, dehydration and shock and their underlying causes are to be treated vigorously with sodium-containing fluids, whole blood, or plasma, and every attempt made to rapidly restore and maintain normal circulating blood volume and electrolyte levels. It takes usually 24 or more hours to establish the existence of anuria in a given patient and during that interval, treatment of shock or dehydration and sodium and fluid loss should be prompt and vigorous. If the circulating blood volume and electrolyte levels have been adequately restored but the patient after 24 to 48 hours still remains in shock *and* anuria, the forcing of intravenous fluids and sodium from this point on is not only ineffective but may, on the contrary, result in overloading of the circulation and fatal pulmonary edema.

Since no one to date has found a satisfactory substance to add to the peritoneal lavage fluid to exert an osmotic effect comparable to that of plasma proteins, appreciable amounts of fluid may be absorbed from the peritoneal cavity with long continuous lavage. This is well demonstrated in Case 4 (M. G.—Table 3—upper nephron nephrosis due to bichloride of mercury) who was lavaged continuously for 9 days and intermittently for 4½ days with a steady decline in the level of the serum albumin from 4.0 to 3.2 Gm. and hematocrit from 33 per cent to 22 per cent. The absorption of fluid from the peritoneal lavage is accelerated if hypertonic intravenous fluids are administered simultaneously.¹³

Hypertonic fluids, such as concentrated salt-soluble human albumin and hypertonic glucose, are contraindicated at all times even if lavage is not being performed due to the fact that they rapidly increase the circulating plasma volume and may precipitate acute pulmonary edema.

The problem of the total electrolyte balance has received little emphasis in the treatment of acute anuria. Our studies suggest that important alterations in the electrolytes occur, some of which can be corrected. Many different types of change may occur early in the course of anuria due to loss of fluid and electrolytes in diarrheal fluid, vomitus, hemorrhage, etc. Late in the course of anuria electrolyte changes due to tissue breakdown may occur. These electrolyte changes are illustrated in Table III, Case 4 (M. G.—bichloride of mercury poisoning). Early in the anuria (5th day) the serum levels of sodium, potassium, calcium and chloride were low, probably due to loss by diarrhea and vomiting which were present. The serum magnesium was high early, the mechanism of this is not clear. It was possible to restore these electrolytes to almost a normal level with peritoneal lavage. The composition of the lavage fluid was varied therefore as the electrolytes, particularly potassium, changed. Figure 5 (Case 4—M. G.—bichloride of mercury poisoning) shows the clearance or retention of electrolytes by peritoneal lavage fluid as compared with the serum electrolyte levels in the same patient. After initial adjustment of the serum deficits or excesses present it is noted that the serum sodium and calcium remained relatively constant. Chloride was absorbed from the lavage fluid throughout indicating a chloride depletion (this patient had nasogastric

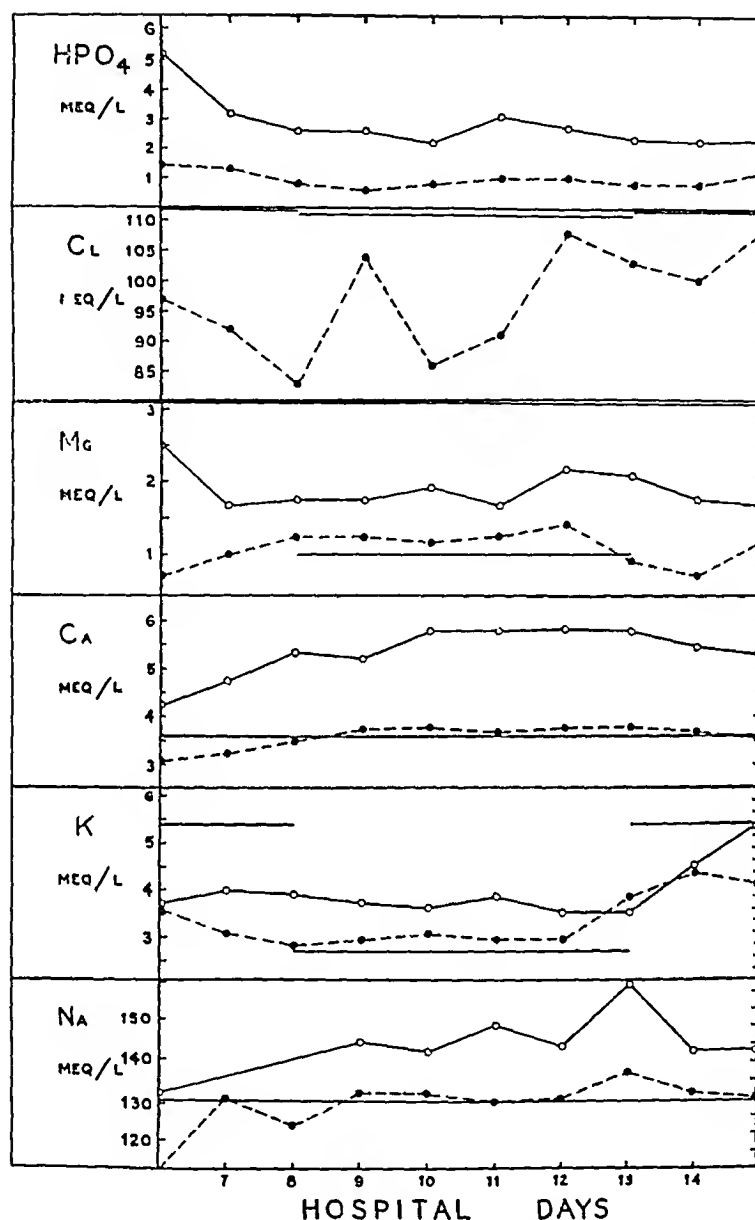


FIG 5—(Case 4, M G—Bichloride Poisoning) Clearance or retention of serum electrolytes by peritoneal lavage

The solid line indicates the concentration in the peritoneal inflow fluid. A change in the position of the line coincides with a change in composition of the inflow fluid.

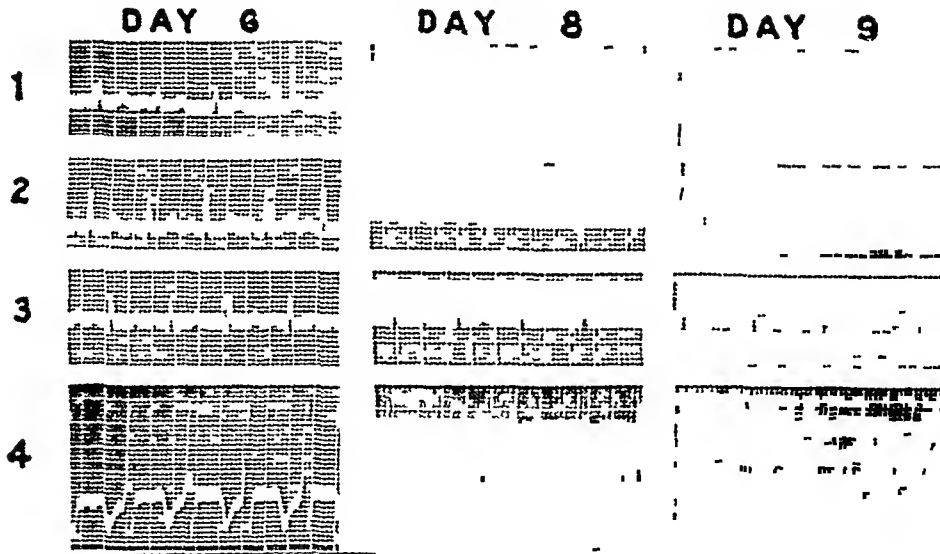
The dotted line with the solid circles represents the concentration in the peritoneal outflow fluid. The line with the open circles indicates the serum concentration.

The serum concentration of chloride is not given as the determinations were made on whole blood.

ACUTE ANURIA

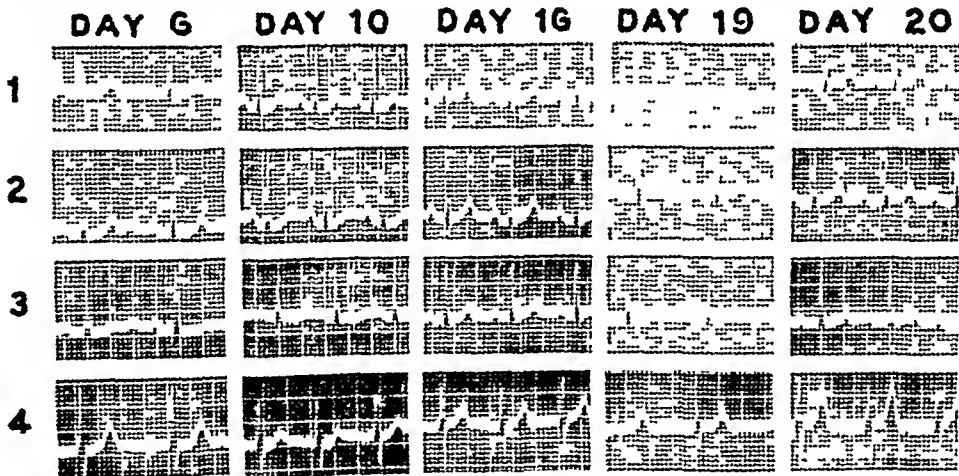
A

CASE NO. 1 W.H



HCO ₃ (MEQ/L)	38	15	9
CA	" 4.0	3.8	4.2
K	" 7.4	9.2	10.5
NPN (MG %)	128	125	128

CASE NO. 4 M.G



pH	7.23	7.48	7.50	—	—
HCO ₃ (MEQ/L)	14	23	23	18	19
CA	" 4.3	5.8	5.0	4.4	4.2
K	" 3.7	3.6	6.6	6.4	7.1
NPN(MG %)	218	71	145	238	230

B

FIG 6—Correlation of the electrolyte changes with the electrocardiogram

suction at intervals) Potassium was retained throughout most of the course (until the 13th day)—the serum levels being low Ringer's-lactate solution was used when the serum potassium was definitely low, and modified Tyrode's solution when the potassium was in the low normal or high normal range. Actually a lavage fluid without potassium should be used when the serum levels are definitely elevated. A drop in the serum potassium occurred with the development of peritonitis, the mechanism of this is not clear. Terminally, the serum potassium levels rose, presumably due to tissue breakdown. The pH of the blood which is known to affect the ratio between serum and cellular potassium concentrations did not appear to be a primary factor in the variations encountered here.

These results demonstrate that the electrolytes vary from period to period and consequently the electrolyte level should be carefully followed in order to properly treat the patient.

If chemical determinations of the electrolytes cannot be made, certain changes in acid-base equilibrium, serum potassium and calcium levels and occasionally magnesium levels may be gauged from their known effects on the electrocardiogram, if serial tracings are taken^{25, 26, 27, 28, 29, 30, 31}. If the T-waves change from normal amplitude to a very low amplitude, it is suggestive of a drop in serum potassium, or, if from normal to high amplitude, a rise in serum potassium is to be suspected. Development of conduction blocks, or of an idioventricular rhythm suggests a very high serum potassium level. A long QT-interval (period of electrical systole) suggests hypocalcemia, although this may also be due to a low serum potassium. Differentiation can usually be made by the height and character of the T-waves.

Electrolyte changes correlated with the electrocardiogram and illustrating these points are shown in Fig 6-A (Case 1—W H) and Fig 6-B (Case 4—M G). The effect of a very high serum potassium (10.5 mEq) on the electrocardiogram is seen in A (Case 1—W H—on the 9th day), where there is a loss of the P-waves, and an intra-ventricular block of the right bundle branch type. The effect of low potassium (3.6 mEq) is seen in Fig 6-B (Case 4—M G) on the 10th day. Here the T-waves are low in amplitude. As the serum potassium increased from 6.6 mEq to 7.1 mEq from the 16th to 20th day, the T-waves became more elevated. The effect of low serum calcium on the QT-interval is seen in Fig 6-A (Case 1—W H) on the 8th day when the serum calcium was 3.8 mEq and the QT-interval 0.34 seconds, compared to a calculated normal of 0.29 seconds.

An important consideration in the treatment of acute anuria is the indication for peritoneal lavage. It is well known that patients with reversible tubular lesions will recover spontaneously provided they are not fatally overhydrated. At present our indications for lavage have narrowed down to the following:

(1) *Hyperpotassemia* Deficits of this electrolyte can be corrected by oral or parenteral administration of potassium chloride, but an excess of potassium ion in the blood must be brought down promptly to a near normal level and this can be accomplished by the use of a proper lavage fluid. (2) *Electrolyte Imbalance* Multiple deviations from the normal electrolyte pattern frequently

can be corrected by the use of a proper lavage fluid (3) *Severe Azotemia*—when it is accompanied by toxic symptoms such as restlessness, disorientation, diplopia, convulsions, generalized twitchings, etc. Any two or all of the above indications may overlap.

Six of our patients received peritoneal lavage. In the first patient (Case 1—W. H.—iodine poisoning) it was a failure due to technical difficulties and fluid retention. Case 5 (B. B.—septic abortion) would have recovered without peritoneal lavage, as would have Case 6 (“X”—transfusion reaction). It did aid in the latter two cases in clearing edema and Case 6 seemed clinically improved, but this is obviously difficult to evaluate. Case 2 (R. O’N.) had an acute glomerulonephritis and probably should not have been lavaged. The role of lavage in Case 3 (H. N.—transfusion reaction) and Case 4 (M. G.—bichloride of mercury poisoning) who received prolonged peritoneal lavage (over ten days) is difficult to evaluate. Both of these patients had good chemical results from the lavage, but died of pulmonary edema, due to too much intravenous fluid.

One advantage of peritoneal lavage is the nutritional one, since glucose is readily absorbed from the peritoneum. This may be important in a patient unable to retain food by mouth, and in whom intravenous fluids must be restricted.

It should be emphasized that peritoneal lavage is not a simple procedure, and if used without expert supervision it may actually contribute to a fatal outcome. All of our patients in whom peritoneal lavage was used for more than a short interval (Cases 1, 2, 3 and 4) developed bacterial contamination of the peritoneum despite the use of penicillin (100,000 units intramuscularly q 3 h). In all the autopsied patients the peritonitis was localized and healing was not considered to be a factor in death. A detailed discussion of various factors in the pathogenesis of the peritonitis is beyond the scope of this report. Strict and continued aseptic technique and avoidance of hypertonic irritating solutions over a prolonged time will minimize but not entirely prevent peritonitis.

ROLE OF VASOSPASM

The role of vasospasm in the production of anuria has been re-emphasized in the work of Trueta.³² Various agents to counteract this vasospasm, such as intravenous alcohol, procaine,³³ spinal anesthesia and splanchnic block,³⁴ have been suggested. We have tried all of these agents. It has been difficult, however, to critically evaluate the results in our patients since other therapeutic agents have been used simultaneously except in Case 7 (W. O’Q.—upper nephron nephrosis) who received intravenous procaine (3 Gm.) on the 3rd and 4th day of his anuria, without any effect on the urine output (Fig. 4). Further critical evaluation of agents to counteract vasospasm should be made.

TREATMENT

As soon as a situation arises, such as dehydration, shock, transfusion reaction, etc., which may precipitate acute anuria every effort is made to correct

the blood volume and serum sodium level. After anuria occurs, all intravenous fluids and sodium are eliminated, with the possible exception of procaine and citrated blood transfusions. If the patient is able to take fluid and food by mouth the oral intake is limited to 500-800 cc of water per day, and a low salt diet, less than 1 Gm per day, is used. The sodium ion is administered only to correct severe acidosis. If the carbon dioxide combining power drops to or below 25 volumes per cent the patient is given small doses of sodium bicarbonate (4 Gm) by mouth with repeated checks of the carbon dioxide combining power.

In these patients with anuria it is well to remember that selective reabsorption and automaticity of maintenance of electrolyte pattern are lacking and that small doses of ions may produce a far greater effect on blood chemistry than would ordinarily occur if renal function were normal.

If the patient is seen in the first 48 hours after anuria develops intravenous procaine is used. 1 Gm in 250 cc of 2½ per cent glucose in water, given over a period of 20 minutes and repeated every 12 hours for 2 to 3 doses.

Penicillin is used routinely (whenever lavage is instituted). Streptomycin and blood transfusions are used as indicated. (In the presence of anuria streptomycin blood level is built up rapidly and should be used with caution). We do not attempt to maintain an adequate protein intake during the critical period of anuria, as this interval is short (10 to 14 days). The restoration of weight and normal nutritional status occurs rapidly after the return of kidney function and has presented no problem. Vitamins C and B₁ are given parenterally.

Daily determination of CO₂, blood chlorides, non-protein-nitrogen, sodium and potassium are made. Close and frequent observations are made for evidence of peripheral pitting edema or signs of pulmonary edema. The decision to institute peritoneal lavage (or gastric lavage) is based on criteria discussed above. The treatment of pulmonary edema, once established, is difficult but venesection with rapid removal of 500 cc of blood has often produced dramatic (although temporary) improvement. Oxygen inhalation under pressure breathing has also been helpful.

During the recovery diuresis phase the fluid and sodium chloride intake are increased to compensate for the increased loss in the urine. It should be re-emphasized that this phase may be a critical one. The urine has a low specific gravity and resembles the glomerular filtrate, the 24 hour urine output may reach 2500 to 4000 cc and large quantities of electrolytes may be lost daily in that volume.

SUMMARY

Six patients with anuria due to potentially reversible tubular lesions were treated with peritoneal or gastric lavage. Three of these patients died and three lived. In addition, one patient who died of an acute diffuse glomerulonephritis was treated with peritoneal lavage. Those who lived would have probably survived without peritoneal or gastric lavage.

Peritoneal lavage was (1) effective in removing substantial amounts of

nitrogenous waste products, (2) helpful in adjusting a disturbed electrolyte pattern, especially potassium, (3) an indirect means for supplying glucose. The disadvantages of peritoneal lavage were (1) a technical procedure which required constant and expert supervision and special nursing, (2) peritoneal contamination (appearance of bacterial organisms in the outflow fluid) in nearly all cases in which lavage was continued for more than four days, (3) absorption of fluid from the peritoneal cavity occurred if hypertonic intravenous fluids were administered simultaneously.

Gastric lavage, used as the primary lavage method in one case, was much less effective in comparison with peritoneal lavage. On the other hand, it did not have the latter's disadvantages.

Acute pulmonary edema was the immediate cause of death in four patients. Six of the seven patients studied developed generalized edema at some stage. These facts emphasize the necessity for rigid restriction of fluid and sodium.

Peritoneal or gastric lavage is used only if the patient shows some deleterious effects from nitrogen retention or electrolyte disturbance, particularly hyperpotassemia.

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GLUCOSE ASSIMILATION DURING ANESTHESIA AND SURGERY*†

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SINCE THE STUDIES OF GRAHAM were reported in 1915,¹ surgeons have assiduously striven to amplify the hepatic glycogen reserve of the preoperative patient. This practice, along with that of parenteral glucose administration in the postoperative state, has yielded benefits so manifest that they need not be recounted here.

In addition to its use before and following operation, carbohydrate is sometimes employed parenterally during operation. There has been no consistency in this practice however, and its rationale has not been established. In the course of our current studies² it occurred to us that parenteral glucose administration during anesthesia and surgery invokes considerations distinctive unto itself.

It is known that anesthesia produced by ether, chloroform, and many other agents, induces a significant hyperglycemia in laboratory animals and humans^{2, 3, 4, 5, 6, 7}. That hepatic glycogenolysis is the source of this hyperglycemia seems evident since it has not been found to occur in Eck fistula or hepatectomized dogs^{5, 9, 10}. Added evidence is supplied by the fact that progressive liver sampling in the ether anesthetized dog shows a decreasing glycogen content^{11, 12}.

In the light of these observations two considerations of clinical import arise. The first relates to the assimilability of parenterally administered glucose during anesthesia and surgery. Since at this time glycogen is being broken down in the liver at an abnormally high rate, as indicated above, the possibility that exogenously supplied glucose cannot be assimilated in appreciable amounts must be entertained. But, if glucose can be assimilated during anesthesia and surgery, it would seem rational to administer it at such time in order to replenish the hepatic glycogen reserve at the very time when it is being drained. Such considerations would seem especially apropos for those patients who come to operation with any degree of inoperable liver damage, as such patients can store only relatively small amounts of glycogen in reserve¹³. In the present study we have determined quantitatively the extent of assimilation of parenterally administered glucose during anesthesia and surgery.

OBSERVATIONS

Twenty-four patients undergoing various surgical procedures were given 1000 cc of 10 per cent glucose in distilled water intravenously during opera-

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tion. Infusions were begun with the onset of surgical anesthesia at the rate of 10 Gm per hour during the first half hour, and thereafter at the rate of 45 Gm per hour until completed, in accordance with a method of glucose infusion previously described.² In some instances glucose infusion was temporarily interrupted for infusion of whole citrated blood. When the infusion time exceeded the operating time, the infusion was continued uninterruptedly after completion of the operation. Among the patients studied various lesions and surgical procedures were represented, and certain patients with laboratory evidence of disturbed hepatic function were purposefully included. None of the patients presented clinical or laboratory evidence of primary impairment of carbohydrate metabolism. All postoperative urines were collected and quantitative sugar determinations made by the method of Somogyi.¹⁴ The balance sheets showing the amount of glucose that was utilized in the procedure (glucose infused minus glucose excreted in the urine) are recorded in Table I.

RESULTS

As may be seen in Table I, 20 of the 24 patients assimilated over 90 per cent of the glucose infused. The remaining four patients assimilated less than 90 per cent, but even the poorest result was 83.6 per cent. The degree to which glucose was assimilated was not related to the anesthetic agent used, nor did it show any consistent relation to the duration of anesthesia and operation, to the state of general hepatic function, or to the presence of acute localized infection. Patients No. 19 and 20, in spite of unabated ketosis at the time of surgery, assimilated 87.1 and 97.4 per cent of the infused glucose, respectively. It might be significant that the former patient presented a history suggesting a longer duration of ketosis than the latter. Only four of the 24 patients in this series (17 per cent) presented immediate postoperative ketonuria, whereas 47 per cent of a consecutive series of 200 patients undergoing operative procedures without concomitant glucose infusion did develop ketonuria.

DISCUSSION

As with all biologic processes, energy must be expended by the liver in performance of its various functions. The hepatic glycogen reserve is important primarily to provide this energy, the preferential fuel of the liver being carbohydrate.^{15, 16} Fats and proteins are utilized very uneconomically by the liver for fuel. Glycogen, on the other hand, becomes available for oxidation without involving dissipation of energy.¹⁷ When the hepatic glycogen reserve is not of amount sufficient to satisfy the full energy requirements of the liver, ketosis develops and, as is well known, many deleterious accompaniments may be associated with this state.¹⁸ Furthermore, the liver, being a relatively anoxic organ, is dependent upon the combustion of available glycogen as a substitute for this anoxia in carrying on its normal physiologic activity.¹⁵

That a rich hepatic glycogen reserve has been found of such great benefit to the surgical patient is quite rational in light of these phenomena. Further consideration would logically indicate that this reserve be available not only

TABLE I

Case	Surgical Pathology	Complicating Pathology	Operation	Anesthesia	Duration of Anesthesia and Surgery	Evidences of Liver Damage	Percent of Glucose Assimilated
1	Carcinoma of breast	None	Radical mastectomy	Cyclopropane-N ₂ O ₂	140 min	None	90.4
2	Chl. cholecystitis	None	Cholecystectomy	Continuous spinal 225 mg procaine	85 min	None	96.0
3	Chl. cholecystitis	Arteriosclerotic heart disease with fibrillation, hepatomegaly	Cholecystectomy	Continuous spinal 300 mg procaine	80 min	Present	95.0
4	Chl. cholecystitis	None	Cholecystectomy	Continuous spinal 250 mg procaine	80 min	None	95.2
5	Chl. cholecystitis	None	Cholecystectomy	Continuous spinal 400 mg procaine	100 min	None	99.0
6	Chl. cholecystitis	Hypertensive cardiovascular disease	Cholecystectomy	Ether-N ₂ O ₂	95 min	Present	95.0
7	Chl. cholecystitis	None	Cholecystectomy	Ether-N ₂ O ₂	110 min	Present	94.7
8	Chl. cholecystitis	Recently subsided acute interstitial pancreatitis	Cholecystectomy	Continuous spinal 300 mg procaine	90 min	None	83.6
9	Carcinoma of gallbladder	None	Cholecystectomy	Continuous spinal 325 mg procaine	140 min	None	97.0
10	Carcinoma of rectum	None	Abdominoperineal resection of rectum	Continuous spinal 350 mg procaine	140 min	None	98.5
11	Carcinoma of rectum	None	Abdominoperineal resection of rectum	Continuous spinal 500 mg procaine	240 min	None	86.4
12	Carcinoma of recto sigmoid	Liver metastases	Abdominoperineal resection of rectum	Continuous spinal 250 mg procaine	145 min	Present	96.8
13	Pancreatic necrosis with abscess formation	Generalized arteriosclerosis	Partial pancreatectomy	Continuous spinal 200 mg procaine	65 min	Present	98.1
14	Hyperthyroidism	Mycrocytic anemia	Hemithyroidectomy (2nd stage)	Ether-N ₂ O ₂	90 min	None	98.0
15	Diffuse non toxic goiter	"Thyroid heart disease"	Thyroidectomy	Ether-N ₂ O ₂	95 min	None	97.6
16	Cholelithiasis	Marked obstructive hepatitis	Cholecystectomy	Continuous spinal 350 mg procaine	180 min	Present	97.6
17	Cholelithiasis	Moderate obstructive hepatitis	Cholecystectomy	Ether-N ₂ O ₂	180 min	Present	100.0
18	Essential hypertension	Early cardiac damage	Thoraco lumbar sympathectomy	Ether-N ₂ O ₂	150 min	None	97.6
19	Acute appendicitis	Ketosis	Appendectomy	Spinal procaine 150 mg	60 min	None	87.1
20	Acute appendicitis	Ketosis	Appendectomy	Spinal procaine 150 mg	60 min	None	97.4
21	Acute appendicitis	None	Appendectomy	Spinal procaine 150 mg	45 min	None	97.4
22	Appendiceal abscess	None	Drainage of abscess	Continuous spinal 225 mg procaine	105 min	None	90.4
23	Incarcerated inguinal hernia	Partial intestinal obstruction, hypertensive heart disease	Herniorrhaphy	Continuous spinal 200 mg procaine	65 min	None	98.2
24	Incarcerated (ventral) hernia	None	Herniorrhaphy	Ether-N ₂ O ₂	103 min	None	86.0

for the impact of anesthesia and operation, but that it be maintained throughout the postoperative period

It would therefore seem rational to supply additional glucose as near as possible to the critical period of operative glycogen breakdown, ideally, during operation itself. Such a procedure, however, would be justified only if it could be ascertained that under the given conditions glucose can be assimilated in appreciable amounts. If not, there would be no advantage to this theoretically desirable procedure and, furthermore, the disadvantage of diuresis would obtain. Certain well established observations, previously discussed, make the assimilability of glucose during anesthesia and operation theoretically uncertain.

The observations reported here show that glucose can be assimilated in quite significant amounts during anesthesia and surgery in patients having no abnormalities of carbohydrate metabolism. Such assimilation has been effected in the presence of prolonged anesthesia, extensive surgical procedures, evidence of diminished hepatic function, and mild degrees of ketosis.

We recognize that most well prepared patients coming to operation will carry an adequate hepatic glycogen reserve through the operative period and until postoperative alimentation is begun. However, since the meticulous pre- and postoperative therapy is for the benefit of the poor risk patient, it is in regard to this group that these considerations find their point. The poor risk patients, from the standpoint of carbohydrate metabolism, in addition, of course, to those with specific metabolic derangements are those with degrees of preoperatively inoperable liver damage. These patients cannot store appreciable glycogen reserves, and when they undergo formidable operations the considerable operative glycogenolysis and difficulties of postoperative alimentation severely drain the previously attained reserve.

SUMMARY

1 Parenteral glucose, administered in accordance with physiologic principles, is well assimilated during anesthesia and surgery.

2 Parenteral glucose alimentation during major operations is advocated to protect the preoperatively attained glycogen reserve. This practice is especially emphasized when there is any degree of preoperatively inoperable liver damage.

The authors wish to express their appreciation for the help and advice of Dr. Michael Somogyi.

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PROPHYLAXIS OF OVARIAN CANCER*

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THE PRESENT STUDY is an attempt to assess the possibility of reducing the mortality from ovarian cancer. Although less prominent in its incidence, cancer of the ovary, because of its low cure rate, ranks fourth among the neoplasms responsible for death in women aged 40 years and over. The mortality rate from this cause among white women beyond the first four decades of life was 17.02 per 100,000 U S population in 1945. During that year 4,386 women died as a result of cancer of the ovary.**

With the inadequate methods of therapy now available, three theoretical possibilities exist for lightening the shadow cast by this disease. These include public education, routine periodic pelvic examinations, and prophylactic ovariectomy.

Little benefit is to be expected from attempts at public education. One of the outstanding features of ovarian cancer is its insidious course and the notorious absence of symptoms until the disease is well advanced. H S Crossen³ forcefully called attention to the silent nature of ovarian carcinoma in 1942 and R J Crossen⁴ (1947) has recently re-emphasized the menace of this characteristic. The onset of symptoms is usually indicative of an incurable stage of the malignant process.

Another possible approach to the problem would be the routine pelvic examination of all women at frequent intervals. It is doubtful, however, whether this procedure will ever be applied to more than a small segment of the population. It is uncertain, moreover, to what extent such a routine would increase the proportion of curable cases. Two recent experiences illustrate the difficulty in recognizing early ovarian cancer and the rapidity with which the tumor may grow.

Case 1—A woman of 45 years had a hysterectomy for myomata associated with menorrhagia. The adnexa appeared grossly normal and were removed only as a prophylactic measure. Histologic examination of the ovaries showed bilateral adenocarcinoma. Seven months later the pelvis was infiltrated with hard masses and the patient died soon thereafter.

Case 2—A postmenopausal woman of 55 years had a vaginal hysterectomy for prolapse. Pelvic examination was otherwise negative. Four months later she returned with extensive and inoperable carcinoma of the ovary, proved at laparotomy.

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** These figures, furnished by the U S Public Health Service, include deaths from cancer of the fallopian tube and parametrium, but the number of such cases is so small as not to affect significantly the statistics.

Accepting the fact that ovarian cancer, once it becomes symptomatic or clinically recognizable, is usually beyond the reach of curative measures, we can anticipate a decrease in the mortality from this disease only by earlier diagnosis or by prophylactic measures. One such approach is currently feasible, namely prophylactic ovariectomy incidental to other operations. Under some circumstances, such as in a postmenopausal woman undergoing hysterectomy, the desirability of prophylactic bilateral oophorectomy is clear-cut and generally accepted. In younger women, however, in whom the cessation of the menstrual function has not yet occurred, castration provides security against ovarian cancer only in exchange for the sacrifice of the still useful endocrine function of the ovaries. Disposition of the ovaries in borderline cases requires individualization.

This problem has been approached through a study of the case histories of the last 260 patients with definite cancer of the ovary in the Sloane Hospital. Attention was focussed on the past surgical history of these 260 patients, to determine the proportion who had had previous pelvic, lower abdominal, vaginal or other relevant operations. This category included operations on the

TABLE I—*Previous Relevant Operations in 260 Patients with Ovarian Cancer**

	Operations	Per Cent
Lower abdominal operations	52	60
Vaginal operations	27	31
Breast operations	5	6
Radiotherapy	9	10
Exploration of adrenal	1	

* Total exceeds the 87 operations mentioned in the text since some of the operative procedures were listed in two categories

breast, because of the close functional relation between this organ and the ovary, pelvic radiotherapy, and a case in which adrenal exploration was performed for a gynecologic complaint (masculinization). These operations present an obligation carefully to evaluate the status of the patient's ovaries, either by direct inspection or by bimanual palpation with the patient anesthetized, and provide an opportunity, if the abdomen is already open, to remove useless or suspect organs.

Among the 260 patients with ovarian cancer were 67 (26 per cent) who had undergone previously 87 such relevant operations. This is a minimum figure and should probably be somewhat higher since several of the charts lacked details of the patient's past history. The operations are grouped and listed in Table I. Fifty-two of them (60 per cent) were lower abdominal operations, in nine of which hysterectomy was performed, twenty-four (28 per cent) were vaginal operations, five (6 per cent) were operations on the breast, and in nine cases (10 per cent) radiotherapy was used, either in the form of intrauterine radium or external roentgen irradiation.

The age of the patients at the time of the original surgical procedure is shown in Table II. Forty-five of these operations (52 per cent) were per-

formed when the patient was aged 40 years or older, and in 17 of these instances (20 per cent) the patient was beyond the fifth decade of life

It is a striking fact that following 29 per cent of the original operations less than two years elapsed until the subsequent operation for ovarian cancer. This interval was five years or less after 39 per cent of the original operations. The distribution of the time intervals is shown in Table III.

TABLE II—*Age of Patients at Original Operations*

Age in Years	Patients
Under 20	4
20-24	7
25-29	2
30-34	15
35-39	13
40-44	13
45-49	15
50-54	7
55-59	4
60-64	4
65-69	1
70-74	1

45
(52%)

17
(20%)

Most of the ovarian neoplasms, as expected, were adenocarcinomas, which comprised 92 per cent of the total. The remaining few tumors consisted of two teratomas, a dysgerminoma, a fibrosarcoma, and a gynandroblastoma.

Because of current interest in the possible carcinogenic effects of radiant energy, and for comparison with a similar tabulation of patients with neoplastic disease of the uterine fundus (Speert and Peightal,¹³ 1949), a listing has been made of the patients in the present series who had had previous pelvic radiotherapy for conditions presumably unrelated to their eventual ovarian lesions. These cases, nine in number, constitute 3.5 per cent of the entire series. Table

TABLE III—*Time Interval Between Original Operation and Subsequent Operation for Ovarian Cancer*

Interval in Years	Patients
Under 1	11
1-2	25
2-3	14
3-4	1
4-5	4
5-10	4
10-15	16
15-20	14
Over 20	4
	19

34
(39%)

IV presents their main features. The patients ranged between 34 and 62 years in age at the time of irradiation, averaging 45.1 years. Five had been treated with intrauterine radium, four with roentgen rays. Their ovarian cancers were discovered between 2½ and 23 years later, the average interval between irradiation and subsequent operation being 9.3 years.

Analysis of the individual cases on which this study is based has brought to light several instances in which conservatism seems to have been overdone, to the detriment of the patient. Some of these cases are abstracted below.

Case 3—This patient underwent a multiple myomectomy at age 40 years. Because of recurrence of her fibroids, hysterectomy and right salpingo-oophorectomy were performed nine years later, at age 49. Six years later routine physical examination revealed an abdominal tumor, which at operation was found to be a hopelessly extensive carcinoma arising from the left ovary. The patient died a year afterward.

Case 4—This patient had her right ovary removed because of a cyst at age 50. Eight years later she complained of swelling of the abdomen and legs. She died in uremia while under study. Autopsy revealed a primary cystadenocarcinoma of the left ovary.

Case 5—This patient had a hysterectomy for fibroids at age 47. Five years later she complained of abdominal pain and vomiting. Exploratory laparotomy revealed an inoperable ovarian carcinoma.

Case 6—This patient had a curettage at the age of 35 years and another at the age of 39, both for menorrhagia. At the age of 43 hysterectomy and appendectomy were performed, presumably for the same reason. A year later she complained of indigestion,

TABLE IV—*Ovarian Tumors Following Previous Pelvic Irradiation*

Patient	Age	Irradiation	Dose	Indication	Interval (Years)	Ovarian Tumor
A	46	Radium	?	Menorrhagia	23	Cystadenocarcinoma
B	51	Radium	?	? Cervical cancer	6	Adenocarcinoma
C	46	Radium	1800 mg. h.	Menorrhagia functional	5	Cystadenocarcinoma
D	62	Radium	1800 mg. h.	Endometrial polyp	2½	Papillary cystadenocarcinoma
E	40	Radium(2x)	?	Myomata	22	No specimen
F	34	X-ray	7 treatments 45 min. each	Ovarian cyst	2½	Papillary cystadenocarcinoma
G	42	X-ray	Artificial menopause	Myomata	10	Papillary adenocarcinoma
H	36	X-ray	Artificial menopause	Postpartum metrorrhagia	9	Papillary adenocarcinoma
I	49	X-ray	Artificial menopause	?	4	Papillary pseudomucinous cystadenocarcinoma

weakness and swelling of the feet. Exploratory laparotomy showed an inoperable cystadenocarcinoma of the ovary.

Case 7—This patient had a supravaginal hysterectomy and left salpingo-oophorectomy for fibroids at age 49. Two years later, complaining of abdominal swelling, she was found to have an inoperable pseudomucinous cystadenocarcinoma. Roentgen-ray therapy prolonged her life another year.

Case 8—This patient had a suspension of the uterus at age 50. Fourteen years later she had a curettage and anterior and posterior colporrhaphy, but there is no record of the examination at that time. A year later she began to complain of abdominal pressure. At operation an adenocarcinoma of the left ovary was found.

Case 9—This patient had a hysterectomy for fibroids at age 46. Fourteen years later, six months after the onset of abdominal swelling, she underwent laparotomy for a tumor of the left ovary which was diagnosed pathologically as a fibrosarcoma. She died four months later.

A second group of cases illustrates the tragedies which may result from diagnostic errors in the interpretation of pelvic masses in middle aged or elderly women. Two such cases are presented below.

Case 10—The patient, at age 71, had a curettage because of a brownish vaginal discharge. A hard, fixed, nodular pelvic mass, extending half-way to the umbilicus, was believed to be a myomatous uterus. Ascites developed soon afterward, and four months later the patient returned with inoperable carcinoma of the ovary.

Case 11—This patient had a curettage for menorrhagia at age 45. A small fixed mass was palpated in the right fornix. The patient died 3½ years later, eight months after operation for a papillary pseudomucinous cystadenocarcinoma of the ovary.

A third category comprises cases in which surgical operations had been performed a short time before the ultimate detection of the ovarian neoplasm, and where careful inspection or palpation of the ovaries at the first procedure might have permitted earlier definitive therapy for the ovarian tumor. Several illustrative cases follow.

Case 12—This patient had a curettage at age 56 for postmenopausal bleeding, but the tissue obtained was insufficient for diagnosis. Description of the pelvic examination was not recorded. Eight months later she complained of abdominal pain. Laparotomy revealed extensive adenocarcinoma arising from the right ovary.

Case 13—This patient had an inguinal herniorrhaphy at age 62. She noticed beginning enlargement of the abdomen three months afterward. In another three months she was found to have an inoperable carcinoma of the ovary.

Case 14—This patient had a radical mastectomy for carcinoma at age 44. A year later she underwent laparotomy because of menorrhagia and a palpable pelvic tumor. Extensive bilateral ovarian carcinoma was present.

Case 15—This patient underwent a left radical mastectomy for carcinoma at age 50 years. A year later she complained of abdominal pain, when she was found to have a pelvic tumor. At operation this proved to be a "melon-sized" papillary serous cystadenocarcinoma of the left ovary.

Case 16—This patient had a curettage at age 45 because of menorrhagia. Pathologic report was endometrial hyperplasia. The record of the examination under anesthesia mentioned only a retroverted uterus. A year and a half later, when vaginal bleeding recurred, now with abdominal pain, the patient was found to have a pelvic tumor. At operation this proved to be a cystadenocarcinoma of the ovary. She died of a pulmonary embolus a week after operation.

Case 17—This patient had an appendectomy at age 48. Sixteen months later she noticed that her abdomen was enlarging. A large inoperable papillary cystadenocarcinoma of the left ovary arose from the pelvis and there was considerable fluid in the abdomen. The patient died six weeks later.

Case 18—This patient had a laparotomy at age 56 for repair of a vesicovaginal fistula which had resulted from an application of radium to the cervix five years previously. There is no recorded description of the internal genitalia. A year later, complaining of abdominal pain, she was found to have massive ascites secondary to an inoperable pelvic carcinoma, probably primary in the ovary.

Case 19—This patient, at age 19, complained of secondary amenorrhea, hirsutism, deepening of the voice, decrease in breast size and loss of weight. Examination showed a masculine habitus, hypertrophied clitoris, and palpably normal uterus and adnexa. Following extensive laboratory study, exploration and biopsy of the right adrenal was performed, all showing no significant pathologic change. Three and a half years later her abdomen began to enlarge. A pelvic tumor was now easily palpable. Following its removal it was classified as a gynandroblastoma. Reoperation a year later and radiotherapy failed to halt the malignant process.

DISCUSSION

The tabulations and illustrative case reports presented above permit certain suggestions for the prophylaxis and earlier detection of ovarian cancer. Twenty-six per cent of our 260 patients with malignant tumors of the ovaries had undergone previous operations which permitted either removal of the ovaries at that time or their inspection or palpation with the patient under anesthesia. This figure agrees well with the 21 per cent incidence of previous relevant operations recently reported by Montgomery¹¹ (1948) in a study of 99 patients with primary ovarian cancer.

It would appear particularly significant that our patients were at least 40 years of age at the time of 52 per cent of the original operations and in 20 per cent of the cases they had already passed their 50th birthday. While few modern gynecologists would subscribe to the radical teaching, espoused a generation ago by Graves, of removing the ovaries in all patients undergoing hysterectomy, there would seem to be little advantage in allowing a woman of 50 years or more to retain her ovaries under circumstances which permit their easy removal.

The lower age limit for prophylactic ovariectomy must remain an individual problem, governed largely by the psychologic status of the patient. There is greater than a one per cent chance that a woman of 40 years will die ultimately of ovarian cancer.* Few women over this age are unwilling to have their ovaries removed incidental to hysterectomy, for example, if the problem is discussed with them beforehand. In unstable or frankly neurotic women, the prospect of an abrupt or premature menopause may well be a reasonable deterrent to such a procedure. The majority of normal women, however, take their climacteric in stride, requiring only a minimum of help from sedative drugs and an understanding physician. Even for the relatively small group of patients for whom endocrine therapy seems necessary, oral estrogens can now meet this need so easily, so effectively, and so economically, as to remove in large measure the fear of the change of life long shared by patient and doctor alike.

Some of the tumors in the present series appeared within so short a time after the original operation as to suggest the possibility at least of their having been present at that time. Twenty-nine per cent of these operations were performed within two years of the subsequent detection of the ovarian cancer and following 39 per cent of the operations the ovarian tumor was discovered within five years. These data reinforce our attitude concerning the desirability of prophylactic ovariectomy when feasible and when acceptable. They permit, furthermore, an enthusiastic endorsement of H. S. Crossen's³ recommendation that "every opportunity afforded by anesthesia for a minor vaginal operation be utilized to make deep accurate palpation of the ovarian areas." We would extend this recommendation to include vaginal examinations for middle aged or elderly women when anesthetized for other operations as well. Pierce and Slaughter (Cancer, 1: 468-471, 1948) have recently reached a similar conclusion in a study of 100 women with breast lesions who were subjected to

* Based on 1945 Vital Statistics of the United States

a gynecological survey. Because of the high incidence of pelvic disease in this group of patients they concluded that it was "the duty of the general surgeon to include a pelvic examination in the investigation of every woman with a breast lesion." About 70 per cent of all ovarian neoplasms are malignant in women over age 50 years (Shands and Clark,¹² 1941), and there is no other simple way to detect these silent tumors in their incipency. Any palpable ovarian enlargement in women of this age group should require laparotomy for its removal. Cases 10 and 11 illustrate the tragedies which may result from misinterpretation of pelvic masses in middle aged or elderly women.

Abundant experimental evidence attests the effectiveness of radiant energy in inducing ovarian tumors, particularly of the granulosa cell type, in mice (Furth and Butterworth,⁶ 1936, Traut and Butterworth,¹⁴ 1937, Geist, Games and Pollack,⁸ 1939, Furth and Boon,⁵ 1947, Lorenz, Eschenbrenner, Heston and Deringer,¹⁰ 1947). The clinical literature also cites several cases in which ovarian cancers have appeared in women subsequent to pelvic irradiation for benign conditions (Werner,¹⁸ 1925, Vogt,¹⁶ 1926, Flaskamp,⁷ 1930, Traut and Marchetti,¹⁵ 1940, Vogt,¹⁷ 1941, Burnam,¹ 1942, Crossen and Crossen,⁴ 1947, Montgomery,¹¹ 1948, Husslein,⁹ 1948). To this group we can add nine additional cases (Table IV). This number constitutes only 3.5 per cent of our patients with ovarian cancer and is significantly less than the 8 per cent incidence of previous pelvic irradiation in patients with malignant tumors of the corpus uteri (Speert and Peighal,¹³ 1949). Moreover, only two instances of ovarian cancer have come to light among a total of 958 patients in whom a radiotherapeutic menopause has been induced in this clinic and who were followed for an average of 6.7 years or a total of 6,402 person-years (Corscaden, Fertig and Gusberg,² 1946). These facts suggest no relationship between ovarian neoplasms and previous pelvic radiotherapy. In 359 patients (37 per cent), however, the follow-up period was less than two years. Our observations, therefore, are not completely satisfactory since radiant energy requires a long latent period, often 20 years or more, for the manifestation of its carcinogenic effect, even on tissues of known susceptibility such as skin. The question must be regarded as unsettled at present. Available data seem to provide no clear evidence that radiant energy is carcinogenic for the human ovary.

SUMMARY

1. A significant proportion of ovarian cancers can be prevented by routine ovariectomy in women undergoing pelvic laparotomy. This prophylactic measure is recommended for most patients over 40 years of age.

2. Among 260 consecutive patients with primary ovarian cancer 26 per cent had had previous relevant operations. These included surgical procedures involving the pelvis, lower abdomen, vagina and breast, and pelvic radiotherapy. The patients were 40 years or older at the time of 52 per cent of the original operations and in 20 per cent they were aged 50 or more. The ovarian tumors were discovered within two years of 29 per cent of the original operations.

3 It is recommended that every opportunity be utilized for pelvic examination under anesthesia of all middle aged or elderly women and that all palpable adnexal masses in postmenopausal women be considered an indication for exploratory laparotomy

4 No causal relationship was found between irradiation and human ovarian cancer

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RATIONALE OF THERAPY IN ACUTE VASCULAR OCCLUSIONS BASED UPON MICROMETRIC OBSERVATIONS*†

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IN A PREVIOUS COMMUNICATION we have described our technic for measuring the changes in caliber of the small vessels of a vascular tree following main stem occlusion¹² All observations were made on mesenteric vessels using a Kniseley fused quartz rod trans-illumination apparatus employing a constant temperature tissue bath with variable volume flow Young, small dogs were used and intravenous nembutal anesthesia was employed A special lucite tray held the dog's mesentery in a nonstretched position, submersed in constantly circulating mammalian Ringer's solution at body temperature The microscope was fixed on small vessels A small precapillary artery and vein running side by side were chosen for observation, the artery measuring from 054 to 144 mm in the various animals and the vein from 090 to 288 mm We found that the behavior of small arteries and veins followed more or less constant patterns of change in caliber pursuant to a main stem occlusion and after its release For purposes of orientation, these patterns will be reviewed briefly

Following clamping of the superior mesenteric artery, both the small artery and vein under observation diminished in caliber After release of the occlusion the small artery remained in moderate spasm for a short period of time before returning to the control caliber This phenomenon we termed residual vasospasm It occurred in the presence of grossly visible reactive hyperemia of the involved intestine

Following clamping of the superior mesenteric vein, the small veins became dilated, while the small arteries exhibited a marked diminution in caliber After release of the venous occlusion, temporary residual vasospasm in the small artery was again noted As the artery returned to its control caliber, the engorged vein also regained its control diameter

These patterns were demonstrated in 110 observations on 61 animals The only differences which occurred were in the extent of change the pattern seemed constant We have termed the diminutions in caliber "spasm" because of certain evidence to substantiate the use of this term Further evidence to support this viewpoint is presented in this paper

The purpose of this report is to describe the variations imposed on these patterns by the actions of certain therapeutic measures in common use today

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All our observations were made by direct microscopic measurement, using a Leitz micrometer installed into the lens system of the microscope. Since we employed direct micrometry, we felt that we might be able to furnish direct evidence pertaining to the influence of various forms of therapy on vessel caliber in acute vascular occlusions. Much of the therapy in vogue today is still controversial, as evidenced by conflicting reports in the literature over the past ten years. Further, there is confusion concerning basic vascular physiology following vascular occlusions. This situation probably exists because most of the conclusions have been arrived at by indirect measurements.

To illustrate one phase of this problem—the question of the existence of venospasm following venous occlusion or thrombophlebitis—we should like to quote from some of the most recent authors.

Allen, Barker and Hines in their recent book on peripheral vascular disease¹ have said

“There seems to be some disagreement with regard to the incidence of arteriospasm in cases of iliofemoral thrombophlebitis. It certainly occurs in occasional cases during the acute phase of the disease and may be so severe that pulsations in the larger arteries disappear for several hours after the clinical onset of the disease. Although some data indicate sympathetic innervation of veins, the theoretic possibility of spasm of venules in cases of iliofemoral thrombophlebitis is not supported by clinical evidence. It is extremely difficult to understand how spasm of the venules can take place in the presence of intense congestion and obvious distention of small veins.”

In his investigations on venospasm, de Sousa Pereira⁷ has indicated that venospasm following thrombophlebitis is responsible for much of the pain. Sympathetic block resulted in relief from venous pain for a period longer than the anesthetic action of the drug employed. This suggested that venospasm may play an important role in the mechanism of pain under such conditions. This author also demonstrated active constriction in the veins in thrombophlebitis. In a recent review, White¹⁸ has stated

“The importance of sympathetic innervation of the veins is still uncertain. While numerous nerve fibers are present in their walls, it is not known how active a role they play in regulating their caliber. Definite dilatation of the veins of patients with thrombophlebitis is clearly shown in contrasting venograms taken before and after procaine block. This clear demonstration of increased venous flow, although most convincing evidence of the therapeutic value of procaine block, does not prove that the increased diameter of the veins is due to release of spasm in their walls. Exactly the same result would follow increased arterial inflow and secondary distention.”

However, White reports that de Sousa Pereira illustrated an increase in caliber of the internal saphenous vein in phlebograms taken before and after the intravenous injection of procaine in a single patient. White comments, “This should not have increased arterial inflow, and, therefore, constitutes fairly convincing evidence that a certain degree of active neurogenic venous constriction may be present.”

In our experiments reported below we measured the caliber of the small vessels following venous occlusion and arterial occlusion in the presence of sympathectomy and compared these measurements with the control pattern. In other experiments we utilized oxygen, papaverine and tetraethylammonium chloride, and made comparable measurements. Observations were also made on the effects of anticoagulants.

We wish to emphasize that our measurements represent vessel caliber only, and no attempt is made in this report to correlate vessel caliber with local blood flow, local blood pressure, local pulse volume or local temperature.

Venous Occlusion

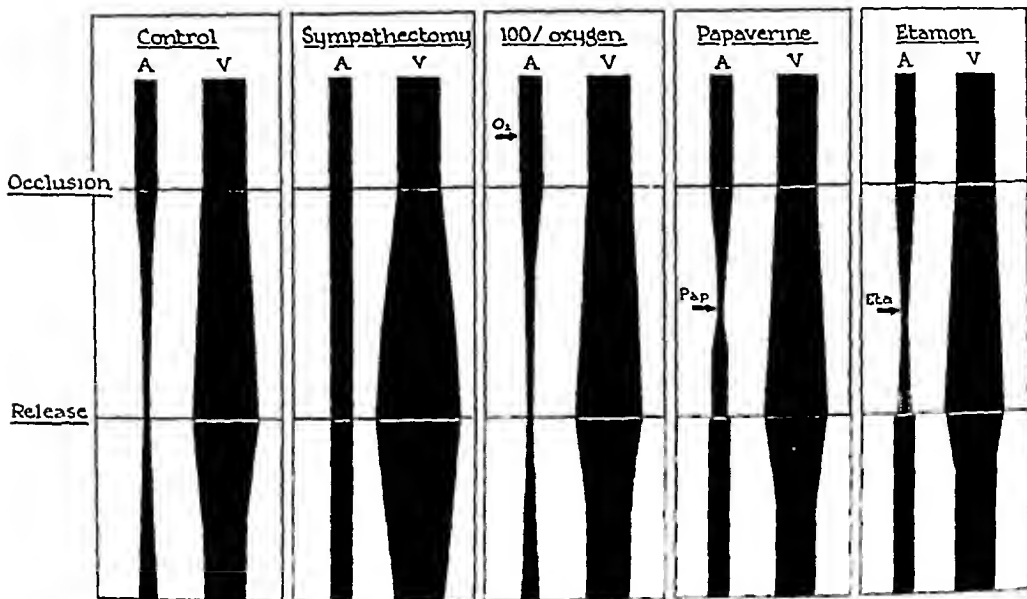


FIG 1—Micrometric pattern of responses in small vessel caliber following acute venous occlusion with various forms of therapy. *Control* After occlusion of main stem vein, the artery (A) goes into reflex spasm while the vein (V) becomes moderately dilated. Upon release of the occlusion, there is a period of residual spasm in the artery while the vein returns to pre-occlusion caliber. *Sympathectomy* abolishes all reflex arterial spasm as well as the residual arterial spasm following release of the occlusion. The vein becomes dilated to a diameter exceeding that of the control during occlusion. *100% oxygen* has no effect on the pattern of vasospasm in venous occlusion (compare with control). *Papaverine*, given during reflex arterial spasm, abolishes some of the spasm. After release of the occlusion there is no phase of residual spasm. *Tetraethylammonium Chloride (Etamon)*, given during reflex arterial spasm abolishes some of the spasm in only 50% of cases (cross-hatched area). After release of the occlusion there is no phase of residual spasm. (See text for further details.)

EFFECT OF SYMPATHECTOMY ON VESSEL CALIBER IN ACUTE VENOUS OCCLUSION

Technic Since all our observations were made on mesenteric vessels, local sympathectomy could be accomplished by the simple expedient of stripping the main stem of the superior mesenteric vessels. It is known that the sympathetic nerves to the mesenteric vascular tree follow the main stem vessels instead of entering the branches in a segmental manner as in the extremities. Occlusions were produced by placing a rubber-tipped clamp on the superior mesenteric

TABLE I—Comparison of Typical Responses in Small Vessel Caliber After Venous Occlusion in Control and Sympathectomized Vessels

CONTROL				SYMPATHECTOMY			
Dog No 14				Dog No 66			
Artery		Vein		Artery		Vein	
Caliber	Per Cent	Caliber	Per Cent	Caliber	Per Cent	Caliber	Per Cent
Pre occlusion reading	100%	162 mm	100%	Pre occlusion reading	100%	108 mm	100%
50 min after venous occlusion	40%	180 mm	111%	41 min after venous occlusion	100%	144 mm	133%
5 min after release of venous occlusion	70%	162 mm	100%	5 min after release of venous occlusion	100%	144 mm	133%
55 min after release of venous occlusion	100%	162 mm	100%	35 min after release of venous occlusion	100%	126 mm	117%
Summary	Maximum decrease in caliber of artery following venous occlusion 40% of pre-occlusion caliber	Maximum increase in caliber of vein following venous occlusion 111% of pre occlusion caliber		Summary	No change in caliber of artery following venous occlusion	Maximum increase in caliber of vein following venous occlusion 133% of pre-occlusion caliber	

vein The controls for this experiment consisted of 33 venous occlusions in unsympathectomized dogs, reported in our previous communication After a control period of observation of about one hour, venous occlusions were made lasting from 30 minutes to one hour 30 minutes Post-release observations were made up to 2 hours 15 minutes

Results Occlusion of the denervated superior mesenteric vein was carried out in 10 dogs In no instance did occlusion result in spasm of the small arteries This finding was in direct contrast to the uniform production of arterial vasospasm which occurred following venous occlusion in the intact specimens

The small veins in the control series were always moderately dilated following venous occlusion In the sympathectomized animals, this dilatation was appreciably magnified

Discussion It appeared that when the nerve fibers were stripped from the vein, reflex vasospasm in the concomitant arterial tree no longer occurred This would support the evidence that the sympathetic fibers associated with veins carry afferent impulses The fact that there was an additional dilatation of the veins following venous occlusion when the nerves were severed, implies that considerable tonus exists in venous occlusion, despite the dilatation by back pressure It is our impression that when the efferent impulses responsible for this tonus can no longer reach the vein wall, additional dilatation is permitted There is no reason to assume the venous pressure in sympathectomized occluded veins is any different from that in intact occluded veins This finding indicates, then, that the sympathetic fibers of veins normally carry efferent impulses also Furthermore, in venous occlusions, the question of whether actual venospasm exists seem dependent upon a balance of two opposing forces (1) the ability of the vein to contract on stimulation of its nerve fibers by the occlusive irritant, and (2) the pressure head of the blood in the blocked venous system Because of the thin muscular coat of these vessels, the latter outbalances the former

It can be inferred from our measurements that interruption of the sympathetic fibers is of value in increasing the caliber of the concomitant arterial tree in acute venous occlusions The fact that sympathetic denervation allows a greater dilatation of an already dilated venous tree might imply a state of increased tonus in the presence of acute venous occlusion, which tonus is released upon denervation

EFFECT OF SYMPATHECTOMY ON VESSEL CALIBER IN ARTERIAL OCCLUSION

Technic The controls for this series consisted of arterial occlusions made on 21 dogs reported previously¹² The main stem of the superior mesenteric artery was stripped of its adventitia and the rubber-tipped clamp was placed in this area after a period of control observation as described above Arterial occlusions were made lasting from 5 minutes to 64 minutes

Results Occlusion of the denervated mesenteric artery was carried out in 14 dogs. The pattern of behavior of the small vessels consisted of no change in caliber of either the artery or vein during the period of occlusion as compared to the pre-occlusion caliber. This was in contrast to the repeated observation of severe spasm in the small artery and moderate spasm in the small vein following arterial occlusion in the unsympathectomized animals.

Upon release of the occlusion there was also no change in caliber of the artery or vein in 9 (64.2 per cent) of the animals. In the remaining 5 animals (35.8 per cent) there was a fleeting period of actual dilatation in the small arteries immediately following release of the arterial occlusion.

Arterial Occlusion

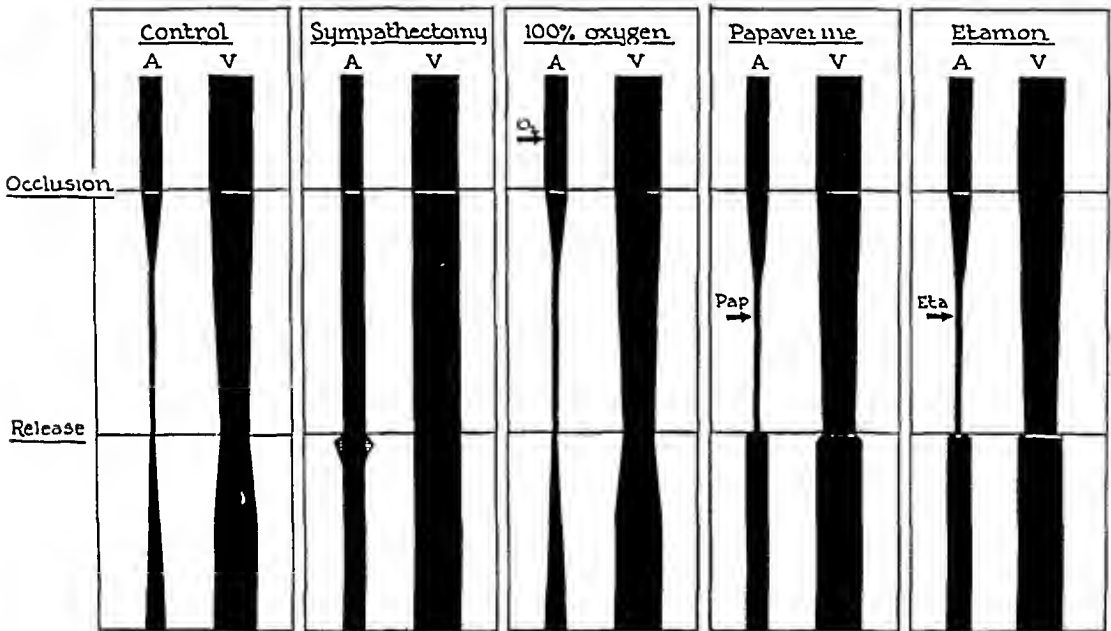


FIG. 2—Micrometric pattern of responses in small vessel caliber following acute arterial occlusion after various forms of therapy. *Control*. After occlusion of the main stem artery, the artery (A) goes into marked spasm while the vein (V) exhibits a mild degree of spasm. Upon release of the occlusion, there is a period of residual spasm in the artery and a similar period in the vein. *Sympathectomy* abolishes all spasm in both artery and vein, during occlusion as well as after release. In some cases, reactive hyperemia is reflected in the caliber of the small artery after release of the occlusion (Cross-hatched area). *100% oxygen* has no effect on the pattern of vasospasm in arterial occlusion. *Papaverine*, given during arterial occlusion, has no effect on arterial spasm. After release of the occlusion, the drug abolishes residual spasm. *Tetraethylammonium Chloride (Etamon)*, given during arterial occlusion has no effect on arterial spasm. After release of the occlusion, the drug abolishes residual spasm. (See text for further details.)

Discussion The fact that there was no diminution in caliber of the small arteries following arterial occlusion in sympathectomized specimens indicates that arterial caliber is not altogether dependent upon blood flow. On the contrary, arterial caliber seems dependent mainly on sympathetic control. In both the control and the sympathectomized animals the artery was completely occluded, and the inflow of arterial blood was reduced to zero in each case.

TABLE II — Comparison of Typical Responses in Small Vessel Caliber After Arterial Occlusion in Control and Sympathectomized Vessels

CONTROL					SYMPATHECTOMY				
Dog No 23					Dog No 16				
Artery		Vein			Artery		Vein		
Caliber	Per Cent	Caliber	Per Cent		Caliber	Per Cent	Caliber	Per Cent	
Pre occlusion reading									
60 min after arterial occlusion	100%	135 mm	100%		090 mm	100%	180 mm	100%	
5 min after release of arterial occlusion	25%	090 mm	67%		090 mm	100%	180 mm	100%	
20 min after release of arterial occlusion	75%	108 mm	86%		090* mm	100%	180 mm	100%	
Summary	Maximum decrease in caliber of artery following arterial occlusion 25% of pre occlusion caliber	Maximum decrease in caliber of vein following arterial occlusion 67% of pre occlusion caliber			090 mm	100%	180 mm	100%	
					No change in caliber of artery following arterial occlusion		No change in caliber of vein following arterial occlusion		

* In 36% of cases there was a fleeting increase in caliber up to 120% of pre-occlusion caliber immediately after release

Diminution in caliber occurred when the nerves were intact, but was absent when the nerves were cut. Consequently it would appear that this response is an active one and dependent more upon the stimulation of the sympathetic reflex arc than it is upon the pressure gradient within the vessels. We therefore feel justified in terming the diminution in caliber *spasm*. If the caliber of the vessel were solely dependent upon blood flow within it, this term would not be justified.

Upon the release of an arterial occlusion in a sympathectomized vessel there may be a period of actual dilatation in about 1/3 of the cases. This dilatation is concurrent with the period of reactive hyperemia. Thus the spasm of small arteries during reactive hyperemia in non-denervated specimens appears to be a compensatory mechanism under the influence of sympathetic control. In the experiments of Eichna and his co-workers⁸ it was found that reactive hyperemia was observed after sympathectomy, but no comment was made as to the extent. The results of our experiments indicate that after sympathectomy, reactive hyperemia might actually be increased in extent.

In summary, our experiments with acute arterial and venous occlusions with and without sympathectomy have indicated that there are afferent as well as efferent fibers in both arteries and veins, and that these fibers are largely responsible for the patterns of response following occlusions. In venous occlusions the pressure gradient of blood flow appears to play a predominant role in deciding the caliber of the small veins, since these vessels are thin-walled and probably do not carry a very heavy sympathetic innervation. On the other hand, the pressure gradient of blood flow in arterial occlusions appears to play a secondary role to the presence or absence of sympathetic stimulation of the arterial tree.

Although it is hazardous to draw parallels too closely between experimental observations and clinical implications, it would appear that the rationale for sympathectomy or sympathetic procaine block in acute venous occlusions is based primarily on the release of reflex arterial spasm.

In acute arterial occlusions, sympathectomy eradicates vasoconstrictor impulses and thereby prevents vasospasm. However, a direct clinical application of this fact may occasionally be fraught with danger. For example, if sympathectomy is performed on a patient whose limb is precariously surviving following an acute arterial occlusion, surgical sympathectomy may reduce blood pressure temporarily, sufficient to endanger the survival of the limb. Two such cases were recently demonstrated.¹⁷ It might be better to apply our findings in such cases as an indicator for repeated procaine blocks to paralyze the sympathetic ganglia, rather than for surgical extirpation. In less crucial instances, sympathectomy would seem to be indicated. A limb which has been the seat of chronic vascular disease for a considerable period of time prior to acute occlusion may benefit more from sympathectomy than an otherwise normal limb suddenly deprived of most of its blood supply.

Sympathectomy directly releases vasospasm, but has only an indirect effect on blood flow. We have observed microscopically several instances in which the rate of flow actually appeared slower following sympathectomy than it did

before The rate of flow bore neither a direct nor inverse relationship to vessel caliber but seemed to depend mainly on other factors, such as blood pressure

Upon the removal of an occlusion from a sympathectomized vessel, there was no phase of residual vasospasm This would seem to substantiate the use of repeated sympathetic blocks after embolectomy

EFFECT OF OXYGEN THERAPY ON VESSEL CALIBER IN ACUTE VENOUS AND ARTERIAL OCCLUSIONS

Technic One hundred per cent oxygen was administered by intratracheal catheter to eight animals with main stem vascular occlusions Four were arterial occlusions and four were venous occlusions In three of the animals (two arterial, one venous) the oxygen was begun before the occlusion In three (two venous, one arterial) the oxygen was given simultaneously with the release of the occlusion In two (one arterial, one venous) oxygen was begun just after the occlusion was made

Results In no instance did oxygen produce an observable effect on the expected responses in vessel caliber during or after release of the occlusion whether it was arterial or venous The pattern of response in the small vessels was identical with that in the animals which received no oxygen

Discussion Some 20 years ago Chase⁴ suggested the use of oxygen inhalation as a therapeutic measure in the revival of strangulated intestine Recently this method was again advocated for the recognition of viability in a loop of bowel whose circulation had been impaired, as well as a form of therapy for the revival of such a segment¹⁴ Our reason for performing this experiment arose from the fact that for many years physiologists have found that oxygen is of no value in the type of anoxia distal to a vascular occlusion (stagnant anoxia) Our observation that oxygen had no direct effect upon the pattern of vasospasm during or after acute vascular occlusions seemed to be at variance with the findings of the recent writers This discrepancy can probably be explained by the assumption that the improvement in color of released strangulated bowel by oxygen inhalation occurred because the patients were under the influence of inhalation anesthesia The diminution in oxygen intake under such conditions would result in a state of anoxic anoxia of a moderate degree Hence in such clinical instances there could be superimposed upon the stagnant anoxia of occlusion, a state of anoxic anoxia It is well known that the administration of oxygen is beneficial in states of anoxic anoxia However, this increased oxygenation of the blood flowing to a given part apparently has no bearing upon the caliber of the vessels in that part A further beneficial effect upon local circulation might perhaps be attributed to better oxygenation of the heart muscle¹⁰ inducing it to improve the general circulatory status of the patient

Thus our findings indicate that oxygen therapy has no effect in dilating the vessels of tissues which have been released from vascular occlusions An improvement in the oxygenation of such tissues might be seen in instances in which there has been a state of anoxic anoxia superimposed Oxygen appears to have no direct effect upon vessel caliber during or after stagnant anoxia

EFFECT OF PAPAVERINE HYDROCHLORIDE ON VESSEL CALIBER
IN ACUTE VENOUS AND ARTERIAL OCCLUSIONS

Technic Papaverine hydrochloride was administered by slow injection into a peripheral vein using $\frac{1}{2}$ grain doses for dogs weighing about 5 kilograms. The drug was administered at the height of arterial vasospasm during the occlusions.

Results (1) VENOUS OCCLUSIONS Papaverine hydrochloride was administered to six animals during venous occlusion. It had a moderate effect in all animals, releasing some, but not all, of the spasm in the small arteries. The drug had no effect if given after the blood had ceased flowing through the small arteries. Once thrombosis of the small vessels occurred, the drug had no effect. The dilating effect of the drug became more pronounced upon release of the occlusion, eradicating the phase of residual spasm which would have otherwise occurred.

(2) ARTERIAL OCCLUSIONS In none of six instances was papaverine found to have an effect on the caliber of the small arteries during arterial occlusion. In two instances of arterial occlusion the injection of papaverine was followed by an increase in the *rate* of flow in the arterial bed in the microscopic field, but there was no effect on the caliber of the vessels. At the conclusion of these two experiments further dissection at the site of application of the occluding clamp revealed that there existed a small collateral vessel proximal to the point of occlusion in each instance.

Once an arterial occlusion was released, papaverine eradicated the phase of residual spasm.

Discussion Papaverine hydrochloride is a drug which apparently acts directly on the muscle fiber within the muscle wall.⁶ Its action is not dependent upon the integrity of the sympathetic nerves. Laufman and Method¹³ have indicated that there was a definite gross color response to therapeutic doses of papaverine following the release of a still viable loop of bowel from strangulation. Our present observations indicate that the drug is of some value in releasing reflex arterial spasm in acute venous occlusions, providing the drug is used before thrombosis of the smaller vessels becomes widespread. It is also of value in obliterating the phase of residual vasospasm following release of vascular occlusion of either the arterial or venous type. The drug is of no value in acute arterial occlusions except when there are collateral vessels proximal to the occlusion which might be dilated sufficiently to carry an additional blood supply to the part. Concerning this point we believe that the collateral vessels in the vicinity proximal to an occlusion respond to the occlusive irritant by reflex spasm at the time of occlusion. Once the vasodilating effect of papaverine is exerted, the collateral vessels can carry a larger load. This could account for the increased rate of flow in the vessels under the microscope in the two cases cited above.

It would appear, therefore, that papaverine should continue to serve as a useful adjunctive treatment in clinical instances of acute venous and arterial occlusions. In venous occlusions it will release some of the reflex vasospasm in

TABLE III—Typical Responses in Small Vessel Caliber After Venous and Arterial Occlusion in Animals Treated with Papaverine Hydrochloride at Height of Vasospasm

VENOUS OCCLUSION				ARTERIAL OCCLUSION			
Dog No 89				Dog No 80			
Artery		Vein		Artery		Vein	
Caliber	Per Cent	Caliber	Per Cent	Caliber	Per Cent	Caliber	Per Cent
Pre occlusion reading	100%	099 mm	100%	Pre occlusion reading	100%	144 mm	100%
28 min after venous occlusion	33%	117 mm	118%	25 min after arterial occlusion	50%	126 mm	87 5%
40 min after venous occlusion and 10 min after papaverine I V	83%	117 mm	118%	40 min after arterial occlusion and 10 min after papaverine I V	50%	126 mm	87 5%
5 min after release of venous occlusion	100%	099 mm	100%	8 min after release of arterial occlusion	75%	126 mm	87 5%
55 min after release of venous occlusion	100%	099 mm	100%	40 min after release of arterial occlusion	100%	144 mm	100%
Summary	Papaverine induced a partial relief of arterial vasospasm in venous occlusion and eradicated residual vasospasm after release of occlusion			Summary	Papaverine had no observable effect on pattern of vasospasm in arterial occlusion		

the small arteries providing it is used before the blood flow in these vessels becomes arrested. In arterial occlusions its value will depend upon the presence or absence of collateral arteries to the part. In either case it should be valuable in eradicating residual vasospasm following removal of an occlusion (*i e*, following embolectomy).

EFFECT OF TETRAETHYLAMMONIUM CHLORIDE (ETAMON) ON
VESSEL CALIBER IN VASCULAR OCCLUSIONS

Technic Tetraethylammonium chloride was administered by slow injection into a peripheral vein using from $\frac{1}{2}$ to 1 cc of the drug for dogs weighing about 5 kilograms. The drug was administered at various stages of arterial vasospasm during both venous and arterial occlusions. It was found that this drug had to be injected very slowly in order to obtain a therapeutic effect. If it was injected too rapidly there was a reversal of effect which will be described below.

Results (1) VENOUS OCCLUSIONS In 19 main stem occlusions we found that tetraethylammonium chloride was able to release the reflex arterial spasm in 10 (53 per cent) of the animals. In these animals the drug was injected equally slowly and therefore we consider these findings valid. In three of the nine remaining animals arterial spasm was unaffected during the occlusion, while in six there was a slight but insignificant response. Upon release of the occlusion in the entire group, the phase of residual spasm was usually eradicated. In one instance the drug was injected immediately upon release of the occlusion with an equivocal result.

Once the shock state became obvious, the drug was found to have no effect on the caliber of the vessels. Moreover, if the drug was injected too rapidly the small vessels exhibited a striking degree of vasospasm within a few minutes. This spasm persisted for as long as 30 minutes or until the animal recovered from the shock state. None of the animals exhibiting this reversal of effect are included in the figures quoted above. As was the case when other therapeutic measures were employed, no effect was noted if tetraethylammonium chloride was injected after circulation in the small vessels became arrested.

(2) ARTERIAL OCCLUSIONS In no instance of eight arterial occlusions was tetraethylammonium chloride successful in releasing the state of arterial spasm. No collateral vessels existed in any of these cases. Once the occlusions were removed, however, the phase of residual spasm was usually eradicated.

Discussion Since the original claims of Berry and associates^{2, 15} were published, several controversial reports⁵ have appeared in the literature. The action of the drug is that of an autonomic blocking agent. It has been suggested¹⁰ that the effect of this drug is roughly proportional to the degree of vasoconstrictor tone and that the magnitude of the response is greater in cases in which the tonus is increased. This concept is apparently tenable where the tonus throughout the entire body is of almost equal magnitude. Deductions from our observations would indicate that this concept must be revised when

applied to local stimulation of vasoconstrictor fibers, as occurs in acute vascular occlusions. We conceive that the drug, by acting upon all ganglia in the body, has a lesser effect upon those ganglia harboring a powerful stimulus from an occlusive irritant than it would have upon normal ganglia. This, in effect, would be a distribution along "paths of least resistance." Thus, in an instance of acute vascular occlusion the action of the drug would dissipate itself throughout the body without being able to "break through" the area in which it was most needed. If its action resulted in a general drop in blood pressure, a harmful effect might result in the area already suffering from a diminished blood supply. If the drug is injected too rapidly and a lowering of the blood pressure ensues, the same effect might result. This was reflected in our measurements by an actual diminution in caliber of already spastic vessels.

In venous occlusions where the afferent stimulation is apparently not very great, we found that the drug has a beneficial effect in approximately 50 per cent of cases. However, in arterial occlusion where there is a much stronger afferent stimulation, the drug in therapeutic doses was not able to induce an increase in caliber of the vessels concerned. When collateral circulation is available the drug apparently has a favorable effect in dilating these channels,⁹ especially if the vessel is sectioned surgically, thus eliminating the presence of an occlusive irritant. In such a case the afferent stimulation of an occlusion-incontinuity is not present. In our arterial occlusions no collaterals existed and the occlusive irritant (clamp) persisted. We feel that our observations on the use of this drug in acute vascular occlusions might help to explain some of the paradoxical effects found in clinical experiences with the use of this drug. A recent report from Mayo Clinic (3) can be interpreted to bear out our concept of the action of this drug in acute vascular occlusion. In this report the drug was found to have a more lasting effect in lowering blood pressure after a Smithwick sympathectomy than it was possible to obtain before the operation, perhaps indicating that a stronger paralyzing effect from a given dose of the drug can be exerted when there are fewer ganglia remaining upon which the drug can act.

The clinical efficacy of tetraethylammonium chloride will depend on the several factors mentioned above.

EFFECT OF ANTICOAGULANTS IN ACUTE VASCULAR OCCLUSIONS

We observed that vasodilating agents could exert their effects on small vessels only when these vessels were free of thrombosis. Although thrombosis did not appear uniformly throughout the small vessel bed, the vessels thus involved would no longer respond to therapeutic measures. Further, we found that we could produce "sludge" at will in the small vessels distal to an occlusion within a relatively short time. We therefore performed a controlled experiment, reported in a previous communication,¹¹ to investigate the effects of anticoagulants on sludge formation as well as on thrombus formation. For this experiment, venous occlusions were used exclusively, since the process was usually more gradual than in the arterial occlusions and could be followed more closely. The results will be reviewed here briefly.

The animals were divided into four groups of six dogs each. Group I consisted of untreated controls in which venous occlusions were produced, Group II received heparin after the appearance of sludge formation, Group III received heparin before venous occlusion, the animals in Group IV were given dicoumerol over a period of three days prior to venous occlusion.

Our observations indicated that sludged masses of blood cells serve as a matrix for thrombus formation, provided the other conditions favoring thrombosis are present. When anticoagulants are administered in doses known to be clinically effective, yet comparatively safe, thrombosis does not generally occur in the small vessels distal to an occlusion, but such doses do not prevent the formation of sludge.

It appears that the administration of anticoagulants prevents thrombus formation in the presence of sludge by preventing the sludged masses of cells from becoming adherent to the endothelial lining of the vessel. Although anticoagulants may cause some diminution in the tenacity of the adherence of the blood cells to one another, sludge formation, as such, is not prevented.

When heparin was used in conjunction with vasodilating measures, the effects of the latter on vessel caliber were not noticeably magnified, but thrombosis in small vessels was delayed. This allowed the vessels to remain patent. If a vasodilating measure exerted an effect, such an effect was noted only in vessels which were patent.

We were struck by the fact that sludge formation usually appeared within 10 to 20 minutes following a venous occlusion, and thrombus formation was noted in some of the small vessels, especially in the capillaries and venules as early as 30 minutes after the appearance of sludge. The importance of early anticoagulant therapy in occlusive vascular states therefore appears obvious.

DISCUSSION

There has been some discussion in the recent literature concerning the interpretation of attempts at generalized vasodilatation as a therapeutic measure in localized vascular disease. DeBakey and co-workers⁵ have revived the "borrowing-lending" phenomenon as an explanation for the behavior of the blood in the presence of localized vasodilatation. They found that tetraethylammonium chloride was unable to relieve pain-induced local vasospasm because the generalized effect of the drug did not result in the shifting of blood to the affected part. The time-honored principle that blood shifts back and forth from one part of the body to the other depending on local needs has been labeled by these authors, "hemometakinesia." Regarding the use of vasodilators within the scope of this concept, they have said:

"Indeed, we have yet to find a general vasodilator which could produce in a local part, such as the toes, fingers, foot, hand or extremity, vasodilatation equal in degree or duration to that produced by sympathetic denervation of this part."

Our observations and measurements support this statement. It is our impression that the active release of a given vasospastic impulse is the primary

feature while the flow of blood into a now larger vascular bed is the secondary feature. Drugs with generalized action like tetraethylammonium chloride acting upon the ganglia or papaverine acting on the periphery, are each considerably weaker in total effect in releasing local vasospastic impulses than is the direct paralysis of the nerves by procaine. However, tetraethylammonium chloride is able to overcome certain mild local vasospastic impulses despite its generalized activity, such as the reflex spasm in some cases of venous occlusion, thus even if its action results in a lowered blood pressure, the temporary block of the ganglion in question may be all that is necessary in some cases to release the spasm. After this occurs, the increased blood flow might suffice to maintain an improved circulatory status to the part.

We certainly agree with DeBailey and co-workers that in doses large enough to equal the effect of a local sympathetic block, tetraethylammonium chloride is dangerous as a shock-producing drug. Similarly, if papaverine is not injected very slowly, it too, causes untoward effects, such as temporary stimulation of respiration and precipitous drops in blood pressure. We noticed further that tetraethylammonium chloride in excessive doses causes fecal and urinary incontinence. The shock state under such conditions would counteract any beneficial measure obtained by the use of generalized vasodilators. We have observed that generalized vasodilators, whether they act upon the ganglion or upon the vessel wall (provided they can reach this area), are too weak in non-shock-producing doses to overcome vasoconstrictor impulses of great magnitude, but are able to release the relatively weaker impulses in some cases.

SUMMARY

Direct micrometry of small vessel caliber was employed to determine the effects of various therapeutic measures on the pattern of behavior of these vessels following main stem vascular occlusions.

Experiments with sympathectomized specimens indicate that the afferent and efferent fibers of both arteries and veins are largely responsible for the patterns of response following occlusions, while the pressure gradient of blood flow through the vascular tree becomes important only when the spastic impulses are weak enough to be overcome by the intravascular pressure. Such a situation accounts for venous engorgement during venous occlusion in the presence of increased tonus in the vein wall.

Oxygen therapy was found to have no effect on vessel caliber.

Papaverine hydrochloride was found to be of value in releasing some of the reflex arterial vasospasm in venous occlusion if used before thrombosis occurred. In arterial occlusions, the drug was of value only when collateral arteries existed above the occlusion. Once an occlusion was released, the drug was able to eradicate residual spasm in the small vessels.

Tetraethylammonium chloride in non-shock-producing doses was able to counteract the vasospastic effects following acute venous occlusion in only 50 percent of cases, while in acute arterial occlusions it was entirely without value. An interpretation of these findings is offered.

Sludge formation is found to occur within a relatively short time after either

arterial or venous occlusion. This phenomenon appears to be a precursor to thrombosis. Heparin and dicoumerol prevent thrombus formation in such cases, but do not alter the character of sludge appreciably. The fact that vasodilating agents are not capable of producing a favorable effect in thrombosed small vessels, implies that the use of anticoagulants be an integral part of therapy in acute main stem occlusions.

Regional sympathetic denervation eradicates the pattern of small vessel spasm to an extent unequalled by the generalized vasodilators employed. However, once an occlusion is released, such generally acting drugs are usually able to counteract residual vasospasm.

Our evidence indicates that the regulation of arterial caliber following occlusions is primarily an expression of sympathetic stimulation and secondarily that of blood flow.

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THE TREATMENT OF CARBUNCLES BY THE LOCAL INJECTION OF PENICILLIN*

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THE PURPOSE OF THIS PAPER is to present the results of a new method in the treatment of carbuncles. The true carbuncle with extensive involvement of the subcutaneous tissue and multiple draining sinuses through the underlying skin presents a surgical problem of major importance. A great many patients suffering from carbuncle are also the victims of diabetes, nephritis, or other debilitating diseases, which on occasion complicate the management and must be treated along with the carbuncle. Carbuncles have been treated by such methods as hyperemia, as suggested by Bier,^{1, 2} injection of antiseptics into their centers,³ ointments,⁴ vaccines,⁵ injection of autogenous blood,⁶ roentgen-ray therapy,^{7, 8, 9} conservative¹⁰ and radical surgery,¹¹ and actual cautery,¹² but the protracted morbidity, the mutilating scarring, and the frequency of complicated sepsis or metastatic pus foci warrant the attempt of new method or methods to prevent these conditions.

Florey and Fleming¹³ in their early work pointed out the fact that penicillin is more efficacious when used locally than when used systemically. This, coupled with Carp's¹⁴ circuminjection of autogenous blood in the treatment of carbuncles, formed the basis of the early work on the method which we are about to describe. So far as we know, this method has not been used before.

During the past three years, we have used this method on many carbuncles. Our present series consists of 20 cases, all of which were large in size. Three of these patients were diabetics. The youngest patient was 11 years of age and the oldest 74, four were females, 16 males. The distribution of lesions is on the accompanying chart. Ten of the lesions were on the neck, four of the lesions were on the lips, three of the lesions were on the hands, one on the buttock, one on the thigh and one on the abdomen. This series of carbuncles was treated only by injection. No roentgen-ray nor incisions were used.

Carbuncle in the diabetic patients requires careful management and cooperation between the surgeon and internist. It is a well-established fact that infection renders the control of diabetes most refractory. McKittrick and Root¹⁵ point out that the logical method of treatment demands immediate control of the patient's ketosis. Needless delay is often spent in futile attempts to control diabetes and limit the inflammatory processes by conservative methods. With the injection method no delay is encountered in limiting the inflammatory process, and the diabetes is more rapidly brought under control.

The method employed consists of the use of penicillin and novocaine. We used 100,000 units of penicillin per cc of 2 per cent novocaine. There is no reaction between penicillin and novocaine, but the solution must be mixed just before using. On occasion the penicillin may precipitate. Five to 20 cc of

* Submitted for publication, October, 1948

this mixture is usually sufficient. The amount, of course, depends upon the size and distribution of the lesion. A very fine hypo needle (24 to 26 gauge) and a lock-type syringe have proved to be the best instruments for delivering the solution. The skin surrounding the carbuncle is carefully cleaned just beyond the indurated area. A small wheal is made in the skin. Considerable pressure is required for infiltration in this area. The needle is then carried into the deeper tissues where the solution may be injected with greater ease. The entire carbuncular area is surrounded. It is necessary to use from three to five points of injection. As the injection is given, one frequently sees necrotic

TABLE I

Pt	Age	Sex	Location of Lesion	Duration of Lesion	Size of Lesion	Number of Injections	Units Penicillin	Hospital Days	Days Lost	
HM	60	M	Neck	5 days	4 cm	2	400 000	5	6	
JW	30	M	Neck	9 days	9 cm	4	600 000	10	19	Diabetic
JC	47	M	Neck	2 days	6 cm	2	400 000	4	10	
CB	28	F	Neck	5 days	6 cm	2	400 000	0	5	
BW	11	M	Lower lip	5 days	3 cm	1	500 000	4	9	
AJ	20	M	Neck	2 days	4 cm	2	400 000	0	4	
WA	21	F	Hand	4 days	2 cm	1	200 000	0	5	
MT	40	M	Buttock	7 days	10 cm	5	1 000 000	10	25	Diabetic
AK	35	M	Lip	3 days	3 cm	1	600 000	4	5	
LE	75	M	Neck	12 days	14 cm	3	1 000 000	5	14	
MB	45	F	Thigh	8 days	14 cm	3	1 000 000	4	10	
TH	50	M	Abdomen	7 days	6 cm	2	500 000	0	3	
BH	45	M	Neck	5 days	8 cm	2	750 000	0	7	
TS	30	M	Lip	3 days	4 cm	3	1 000 000	7	14	Diabetic
MO	28	M	Hand	4 days	3 cm	1	500 000	0	1	
TJ	34	M	Lip	2 days	3 cm	1	1 000 000	4	4	
BR	60	M	Neck	7 days	12 cm	4	1 500 000	3	8	
LW	35	M	Hand	4 days	5 cm	1	300 000	0	2	
JM	30	M	Neck	5 days	8 cm	1	1 000 000	5	10	
EB	56	M	Neck	7 days	8 cm	2	1 600,000	0	2	

material exude from the center part of the lesion. Attention is called to the fact that the solution is not injected into the carbuncle, but around it, just beyond the indurated zone. Hot packs are recommended and the patient is seen daily. We have not found it necessary to anesthetize any of the patients in this series.

Figure 1 is a semi-diagrammatic explanation of the method employed.

The mode of spreading of a carbuncle is shown in Figure 2. The mode of spread also explains how the penicillin is able to attack the lesion directly. The column of Warren rests on the fascia. These structures are surrounded by a cell-like cuff, which just under the skin has a small defect, a festoon-like curve which connects the adjacent adipose column. It is through the openings below the skin, the adipose columns, and along the fascia that the infection spreads. By the same route the penicillin is able to reach the septic focus.

A typical course of a carbuncle of the neck treated in this manner is as follows. Immediately following the injection the patient is able to turn his

head, and frequently says, "This is the first time I have been free of pain in several days." He gets off the table without aid, and his entire expression has changed. Usually there is no tenderness at the site of injection. The carbuncle at this point shows pus exuding from the small openings. On the second day drainage is usually rather profuse. This drainage persists two or three days longer, depending upon the size of the lesion. A few of the openings coalesce, and healthy red granulation tissue is seen in the depths of the lesion. Epithelization is rapid. The resulting scar is thin and white, not adherent to the surrounding tissue. The induration subsides and is usually gone within two to four weeks.

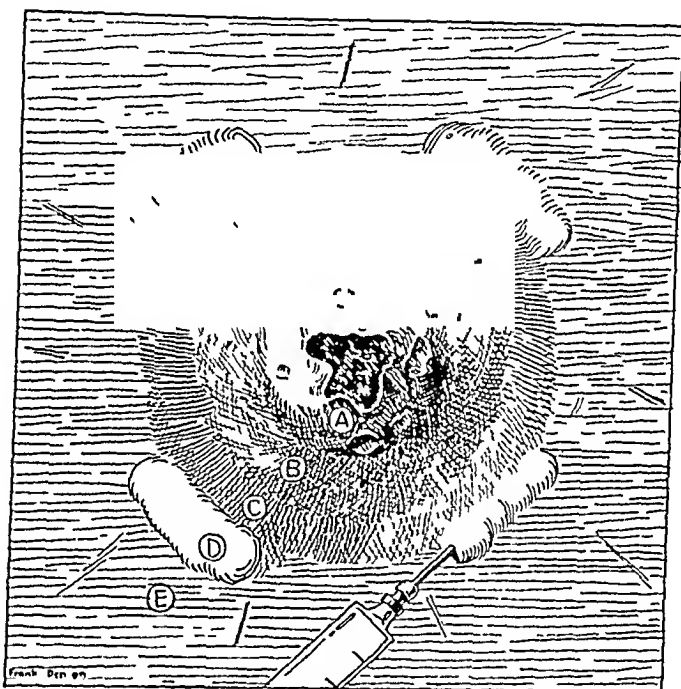


FIG 1—Semi-diagrammatic drawing of the various zones of a carbuncle

- A Represents the necrotic and drainage area
- B Slightly bluish and congested area
- C The indurated area
- D The wheal of penicillin and novocaine. At the completion of the injection, these wheals will be continuous. (After Kanavel)¹⁶

A Typical Case History The last case listed on the chart reads as follows: E. B., on March 9, 1948, a 56-year-old farmer was referred to us complaining of a large carbuncle of seven days' duration on the neck. He had received no treatment whatsoever. The temperature was 99.6°, white blood count 18,600, 74% pmn. The urine was negative. The carbuncle measured 8 cm in diameter. There were four draining sinuses and a small amount of pus present. Eight hundred thousand units of penicillin and 8 cc of novocaine were injected into the area surrounding the carbuncle. Relief from pain was immediate. The patient was seen the next day, at which time the carbuncle was less painful. The patient stated that he had slept for the first time in a week. The carbuncle was draining profusely. Another injection of 800,000 units of penicillin and novocaine

was made in the area surrounding the carbuncle. The patient was seen the following day. The carbuncle was now soft, non-tender and not red. Drainage had all but disappeared. On March 16th, seven days after the first treatment, the carbuncle had healed. Epithelization was complete and there was a minimal amount of induration surrounding the original lesion. The patient stated that he had lost only two days of work.

By using this method, we have been able to shorten the morbidity of patients suffering from carbuncle. The tabulated chart shows the number of hospital days and the number of days actually lost from work. The average hospital stay in this series was three days. In spite of the size of the lesion

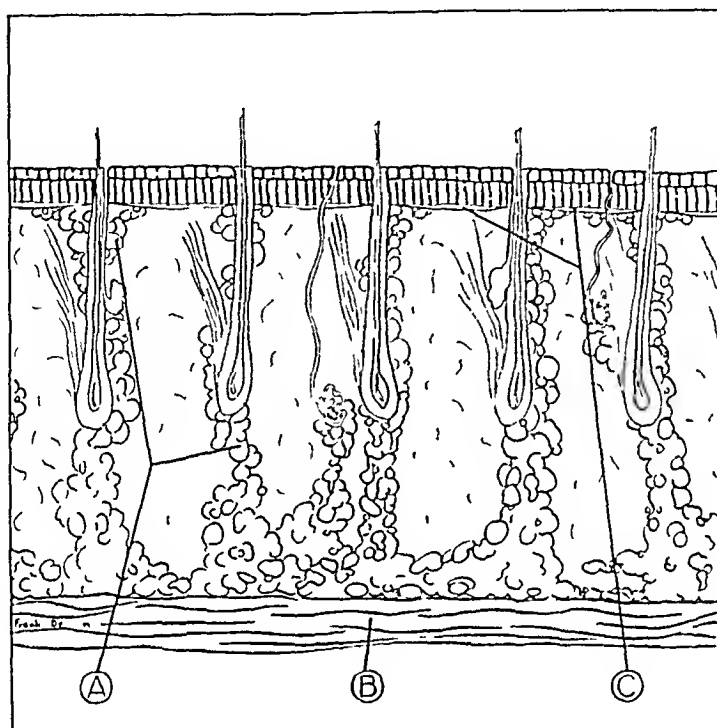


FIG 2—Semi-diagrammatic drawing of the gross section of skin and subcutaneous tissue
A The fat columns of Warren
B The fascia
C Festooning cuff at the top of the columns of Warren

many of these patients were not hospitalized. In two instances the treatment was started at home. Otherwise the treatment was carried out as an office procedure. The average number of days lost in this series was 8.6. A great many of our patients returned to their jobs before epithelization was completed. They were able to do their own dressings, thereby cutting down the amount of time lost. There was no mortality in this series. This method may be employed at any stage of the disease, which is in contradistinction with the use of roentgen-ray in the treatment of carbuncles. After the time the slough begins to appear, roentgen ray is not efficacious. Surgical therapy is then often employed. None of the cases in our series failed to respond to the injection of penicillin, and no reaction to the treatment was encountered.

SUMMARY

1 A new method for the treatment of carbuncle has been presented This may be used at any stage of the disease The relief from pain is immediate The method is simple and may be used as an office procedure

2 A series of 20 cases treated in this manner with their results were given There were no deaths in this series and no recurrence of the infection locally The average hospitalization was three days and the time lost from work was 8.6

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COMPLETE EXCISION OF PELVIC VISCERA IN THE MALE FOR ADVANCED CARCINOMA OF THE SIGMOID INVADING THE URINARY BLADDER*

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In a previous communication¹ a procedure was described for complete excision of the pelvic viscera for advanced carcinoma in the pelvis of the female in which there was involvement of uterus, bladder and rectum. The excretory functions of the alimentary and urinary tracts were provided for by an end sigmoid colostomy proximal to which there was bilateral implantation of the ureters (into the sigmoid). In the series of 22 instances reported, one of the cases listed was that of a male in whom a carcinoma of a redundant loop of sigmoid colon had infiltrated the urinary bladder beginning at the dome and extending downward toward the base. A segment of the lower ileum was also included in the carcinomatous mass. Because the situation in the male presents a number of problems different from that in the female, it is deemed justifiable to report the case in the male somewhat in detail since in the report cited above this patient was simply mentioned as an example of a successful case.

CASE HISTORY

M P, male, age 46 years. Admitted to the private service of the writer at Memorial Hospital, January 2, 1948. In February, 1947, he had been seen in another institution where laparotomy had been performed for a carcinoma in the sigmoid colon. At this time a rather large carcinomatous mass in a redundant sigmoid was discovered to have attached itself to the dome of the urinary bladder. There were no liver metastases. There was no peritoneal spread but because of the attachment to the urinary bladder the situation was deemed inoperable. To relieve obstruction a double barreled colostomy was performed at about the junction of descending colon with sigmoid colon. Following this operation the colostomy functioned satisfactorily but there were severe cramping pains in the abdomen necessitating rehospitalization on three occasions. In general, the patient was unable to carry on his usual occupation. In the fall of 1947, the patient experienced several episodes characterized by severe chills and rise in temperature to 102° to 104°F. This resulted not only in discomfort at the time of the episode but there was marked general discomfort and feeling of disability for some days following the return of the temperature to normal.

Physical examination revealed a rather emaciated male of stated age. The patient seemed rather nervous and very easily upset emotionally.

General physical examination of the abdomen revealed no evidences of ascites, periumbilical cutaneous metastases or enlarged inguinal nodes. The double barreled colostomy in the left lower quadrant was satisfactory. The muscles of the abdominal wall seemed to be held rather rigidly although there was no pain on superficial or deep palpation. The liver was not palpable. Rectal examination revealed at the tip of the examining finger a firm, rather fixed mass which could not be directly palpated within the lumen of the pelvic colon. This mass seemed fixed to the bladder anteriorly and could not be moved easily in relation to the sacrum. No discreet nodules were palpated in the cul-de-sac.

* Submitted for publication, October, 1948

Laboratory examinations were as follows Plasma proteins 6.9 Gm %, B U N 8.9 mg %, W B C 8,800, Hemoglobin 13 Gm, Urinalysis albumin 4+, sugar 0, many leukocytes Roentgenographic study of chest No evidence of pulmonary metastases

Operation (Figs 1A and 1B) January 10, 1948 Ether anesthesia (with curare)
Assistants Drs T Walsh and H J Vandenberg

A low midline incision was made to enter the abdomen There was no free fluid nor immediate evidence of peritoneal metastases The liver was palpated and inspected and was free from metastases The spleen was not enlarged Several large, soft, peri-aortic nodes were palpated and one at about the level of the umbilicus was excised and sent for frozen section diagnosis The report was returned as showing no evidence of metastatic carcinoma

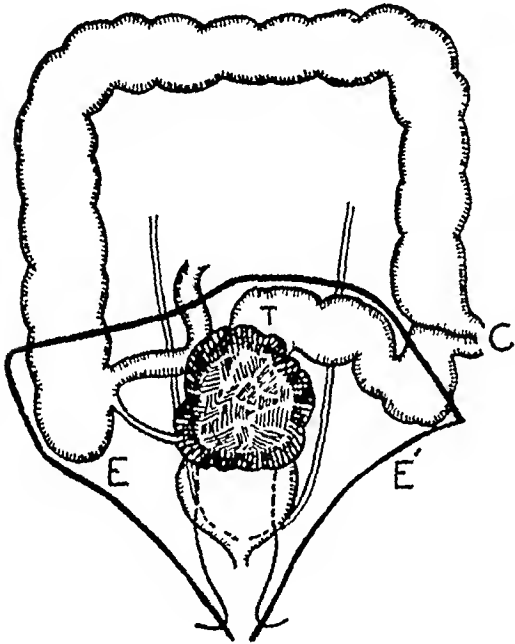


FIG 1—A Diagram showing T, carcinoma arising in redundant loop of sigmoid that has invaded dome of urinary bladder, tip of appendix and loop of ileum C, double barrel colostomy performed a year previously Lines E, E', indicate extent of operation (See Text)

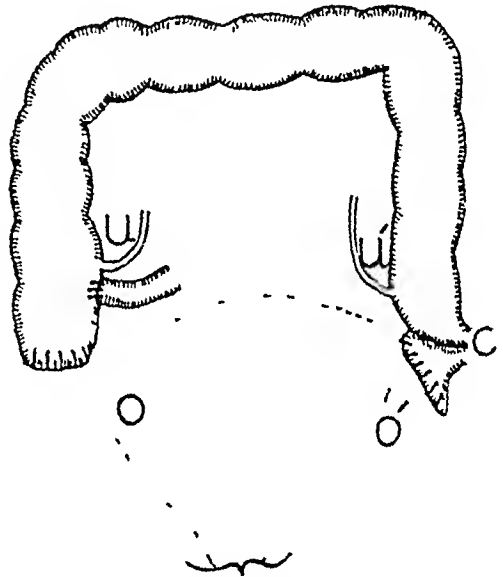


FIG 1—B Diagram illustrating postoperative condition U, right ureter implanted into ascending colon above ileocolostomy U', left ureter implanted into lowest segment of descending colon above colostomy, C, O, O', area denuded of peritoneum after excisions described

In the lower abdomen a large rounded mass, obviously a carcinoma, surrounded by considerable inflammatory reaction was found Coursing into the upper portion of this mass the loop of sigmoid colon below the double barreled colostomy could be traced but in the mass it seemed to lose its identity A segment of lower ileum about 10 cm in length also was attached to the mass on its upper right aspect Palpating inferiorly the mass seemed to be continuous with the dome of the urinary bladder Palpation downward into the true pelvis on each side of the mass and bladder revealed no infiltration between the mass and bladder on the one hand and the sides of the pelvis It also was noted that the appendix seemed to be pulled into the mass and was stretched rather tightly

While the mass was being palpated and moved from one side to another to determine any extensions into posterior abdominal wall or lateral pelvic walls, a separation was made on its superior surface with escape of about 30 cc of thick, yellow pus with typical fecal odor It became obvious that in the center of the mass there was an abscess that had

been inadvertently opened. The pus was sponged away as quickly as possible and gauze plugs were placed into the tear.

Both hypogastric arteries and veins were isolated, doubly ligated and transected. Arterial and venous branches coursing downward and forward toward the bladder and the lower pelvic colon were likewise isolated, ligated and divided. The peritoneum at the level of the pelvic brim was incised and by digital and gauze dissection it was elevated toward the midline all the way around. The peritoneum reflecting from the anterior abdominal wall onto the anterior aspect of the bladder was incised and by means of gauze



FIG 2—Photograph of surgical specimens. M, large neoplastic mass including pelvic and sigmoid colon, urinary bladder (and lower ureters and prostate). E, segment of lower ileum invaded by neoplasm. A, anus. C, caecum and lower ascending colon. I, small segment of ileum just proximal to caecum.

and digital dissection the mass and bladder were freed from the inner surfaces of the symphysis pubis and adjacent portions of the bony pelvis. Continuation of this dissection all the way around including the hollow of the sacrum resulted in mobilization of the mass which consisted of tumor, lower sigmoid and pelvic colon and urinary bladder from the sides of the pelvis in all directions. The only attachments remaining were superiorly with the sigmoid and ileum and inferiorly on the urogenital diaphragm.

The sigmoid colon, about 6 cm below the double-barreled colostomy, was transected and each end invaginated by purse string suture. This resulted in a small segment of sigmoid remaining as the lower limb of the double-barreled colostomy in the left lower quadrant. The mesosigmoid was transected at its origin and the large vessels secured and



FIG 3—Mass M, shown in Fig 2, has been bisected. E, segment of lower ileum. S, sigmoid and site of primary growth. B, urinary bladder, P, prostate. C, neoplasm with necrotic center (abscess). Extensive invasion of posterior bladder wall is shown. A, anus.

ligated. Mobilization of the lower ileum and cecum was then begun by elevation from the posterior abdominal wall. The segment of ileum involved in the mass was isolated and divided between clamps. In isolating a triangular portion of mesentery corresponding to this segment of ileum, large vessels going to the cecum were transected and ligated. In

a few moments the cecum became somewhat cyanotic and it was deemed necessary to excise this also. The cecum and lower half of ascending colon were then completely mobilized and the ascending colon transected in its mid portion, the upper segment being invaginated by a triple row of sutures. The ileum was then anastomosed to the ascending colon end-to-side.

Both ureters could now be well inspected and were found not dilated nor involved by neoplasm above the pelvic brim. The ureters were transected at about the level of the fourth lumbar vertebra. The right ureter was implanted into the upper portion of ascending colon by means of a modified Coffey I technique. The left ureter was implanted into the descending colon about 6 cm. above the colostomy also by a modified Coffey I technique. The abdominal wound was then closed in layers with soft rubber drains in the inferior angle of the wound.

The patient was then placed in lithotomy position and an elliptical incision made about the anus after the latter was closed with purse string suture. It extended forward on the right side of the base of the scrotum a little farther than would ordinarily be the case in the usual combined abdomino-perineal resection. The levator ani muscles were divided and the anal colon completely mobilized.

Dissecting with scissors the lower portions of the pelvic colon were then liberated first on the right and then on the left side by division of musculo-fascial attachments of the pelvic floor.

The urethra was transected as it emerged from the inferior portion of the prostate. The inferior and lateral attachments of the latter were divided completely.

The bladder, prostate, anal, pelvic and sigmoid colons with tumor mass and attached segments of ileum were removed through the pelvic floor.

The defect in the pelvic floor was closed by interrupted catgut sutures for the muscles and fascia and a separate layer of catgut sutures for the skin and subcutaneous fat. A hard rubber tube drain was inserted through the repaired pelvic floor to drain the lower true pelvis.

Duration of operation Five hours

Fluids administered intravenously 5000 cc blood, 1500 cc plasma, 1500 cc normal saline, 500 cc 5% dextrose

Gross pathologic study See accompanying Figs 2 and 3

Histologic diagnosis Adenocarcinoma of colon with invasion of bladder, ileum and metastases to lymph nodes in meso-sigmoid

The postoperative course was prolonged and complicated by the development of deep pelvic abscess and abscesses in the abdominal wall. However, urinary and fecal drainage from the colostomy was satisfactory from the day after operation. Intravenous pyelograms taken on the 19th day after operation showed moderate bilateral hydronephrosis.

On the third day after operation the B U N was 40.3 mg % and thereafter progressively fell to 15.1 mg % on the day he was discharged. The patient left the hospital on the 39th day after operation, ambulatory, free from abdominal pain and with no fever.

Since discharge he has gained 25 lbs in weight.

At this writing, one year and two months after operation, he is returned to his usual occupation, that of a merchant, and wears a Rutzen bag over the colostomy (sealed to the skin). Physical activities are essentially normal. He is without pain, and has taken business and pleasure trips.

DISCUSSION

The successful outcome of the operation with return to his usual occupation and relief from pain and episodes of chills and fever of urinary tract origin, illustrates again the palliation that is sometimes possible in the face of desperate situations that may be encountered at the time of laparotomy. One year prior to the operation described, this patient presented the criteria of advanced and

"inoperable" carcinoma The case record also illustrates again how certain abdominal neoplasms (of the colon in this instance) may progress locally to a marked degree before liver metastases may become manifested Finally, the feasibility of complete excision of pelvic viscera in the male has been demonstrated as a counterpart of the procedure devised for advanced pelvic cancer in the female

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ADAMANTINOMA OF THE MANDIBLE*

A CASE REPORT

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AN ADAMANTINOMA is a rare epithelial tumor arising from the enamel organ either in the mandible or maxilla. This slowly growing tumor is locally malignant (similar to a basal cell epithelioma of the skin) and on rare occasions has been noted to metastasize. A review of the medical records of the Memorial Hospital for the 21-year period 1927 through 1947 reveals that 51 patients received treatment for adamantinomata, in each case the clinical diagnosis was confirmed by histopathologic examination of the tumor tissue. The disease was found in 27 males and 24 females. The mandible was the site of origin of the tumor in 42 cases and the maxilla in nine cases. Two of the adamantinomata metastasized, one to a regional lymph node, the other systemically to the lungs resulting in death to the patient.

A detailed discussion of adamantinoma (its clinical characteristics, histopathology, treatment, and review of the literature) is not the intent of this report. It is sufficient to state that our treatment of this tumor during the past 10 years or more has been by radical surgical removal. In the lower jaw, partial resection of the mandible is usually required. In the upper jaw, removal of one maxilla (sparing the floor of the orbit) is the procedure of choice.

The purpose of this paper is to report the surgical management of one patient with a very extensive adamantinoma of the mandible. The case is of unusual interest for two reasons: (1) the tumor was of sufficient size to require resection of the entire mandible in one stage; (2) There was a solitary metastasis to a regional lymph node.

CASE REPORT

J. C., a 32-year-old Negro, came to the Memorial Hospital on Dec. 21, 1946, complaining of a "lump" in the jaw of 6 years duration. Being a part-time professional boxer, the patient naturally (and erroneously) believed his tumor was caused by a punch on the jaw. Four years ago, a partial removal of the tumor was attempted through a submental approach. Following this operation the tumor continued to grow. The patient stated his general health was excellent.

Examination. A well developed, healthy appearing Negro, with a huge 15 cm. bony tumor of the mandible extending from the second molar tooth on the right to the second bicuspid tooth on the left (Fig. 1). The overlying skin was freely movable, two areas of superficial ulceration were noted in the mucosa of the right lower gingiva. The most unusual finding was a 4 cm., rubbery, freely movable left posterior submaxillary lymph node (Fig. 2).

Clinical Diagnosis. Adamantinoma of mandible, with possible metastasis to left submaxillary lymph node.

* Submitted for publication, December, 1948.

Laboratory Data Biopsy of tumor of mandible Adamantinoma Aspiration biopsy of left submaxillary lymph node Metastatic adamantinoma Roentgen-ray film of chest Essentially normal

Blood Mazzini Negative for syphilis

Submitted roentgen-ray film report of mandible "Multicystic process involving a great deal of the mandible on both sides of the symphysis"

The patient was admitted to the hospital on January 14, 1947 On January 17th a total mandibulectomy and bilateral submaxillary neck dissection was performed

Operative Procedure A preliminary tracheotomy was made under local 2% Monocaine anesthesia The patient was then anesthetized with intravenous pentothal (2.5% solution), oxygen being supplied by a closed respiratory system through the tracheostomy



FIG 1



FIG 2

FIG 1—Full face preoperative appearance (December, 1946)

FIG 2—Left lateral preoperative appearance (December, 1946) showing metastatic node in left upper neck

tube The lower lip was split with two vertical incisions 2.5 cm apart, each incision being carried posteriorly across the submaxillary triangle to the anterior margin of the sternocleidomastoid muscle on each side (Fig 3) Flaps composed of skin, subcutaneous fat, and platysma muscle were then developed and reflected laterally, exposing both submaxillary triangles (Fig 4) An enlarged lymph node was noted in the left posterior submaxillary area The external carotid arteries were identified on both sides and were ligated with steel wire just distal to their superior thyroid branches Both submaxillary triangles were then cleaned out including the submaxillary glands, the soft tissue of this dissection remained attached to the mandible superiorly

The hypopharynx was packed with gauze and the operative incision carried into the mucosa of the oral cavity around the tumor (Figs 5 and 6) The right mandible was disarticulated by dividing the masseter, pterygoid and temporal muscles and finally the capsule of the temporomandibular joint The muscles in the floor of the mouth were severed from the mandible The left mandible was disarticulated in a manner similar to

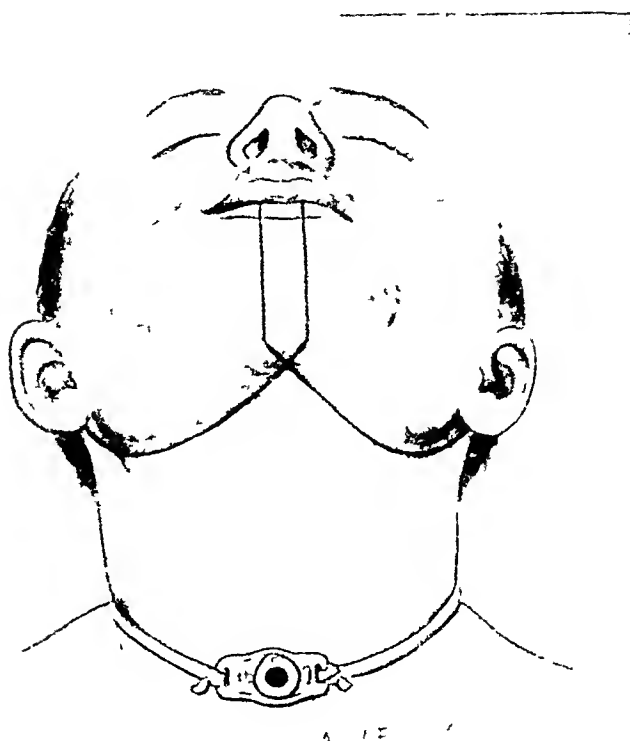


FIG 3—Skin incision showing removal of a central segment of lower lip. Note tracheostomy tube in place.

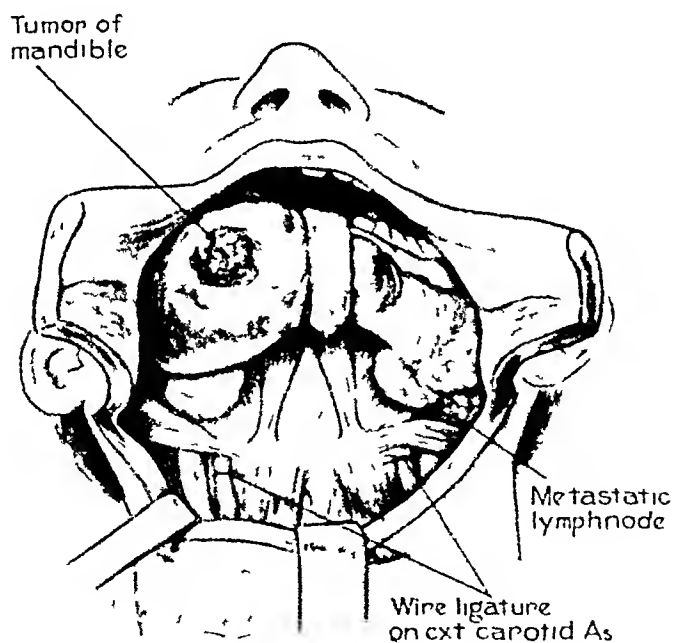


FIG 4—Skin flaps retracted revealing tumor of mandible and metastatic node in left neck.

the right side* The operative specimen consisting of the entire mandible and the contents of both submaxillary triangles was removed en masse (Fig 7)



FIG 5—Intra-oral appearance of tumor

* When a major portion of the mandible must be resected and immediate plastic reconstruction of the bony defect is not desirable, experience has shown us that disarticulation at the temporomandibular joint is preferable to leaving a portion of the ascending ramus in place. Any remaining fragment of the mandible is displaced upward by the pull of the temporal muscle and medially by the action of the internal pterygoid muscles. In such a position the ascending ramus is useless for mastication while its medial displacement into the oral cavity often causes some interference with the normal act of deglutition. This disadvantage can be eliminated by disarticulation of the mandible.

The complete removal of a malignant tumor of the mandible is of much greater importance to the ultimate prognosis than a fine cosmetic end result. Therefore, we seldom attempt an immediate plastic repair of the operative defect.



Fig 7—Operative specimen

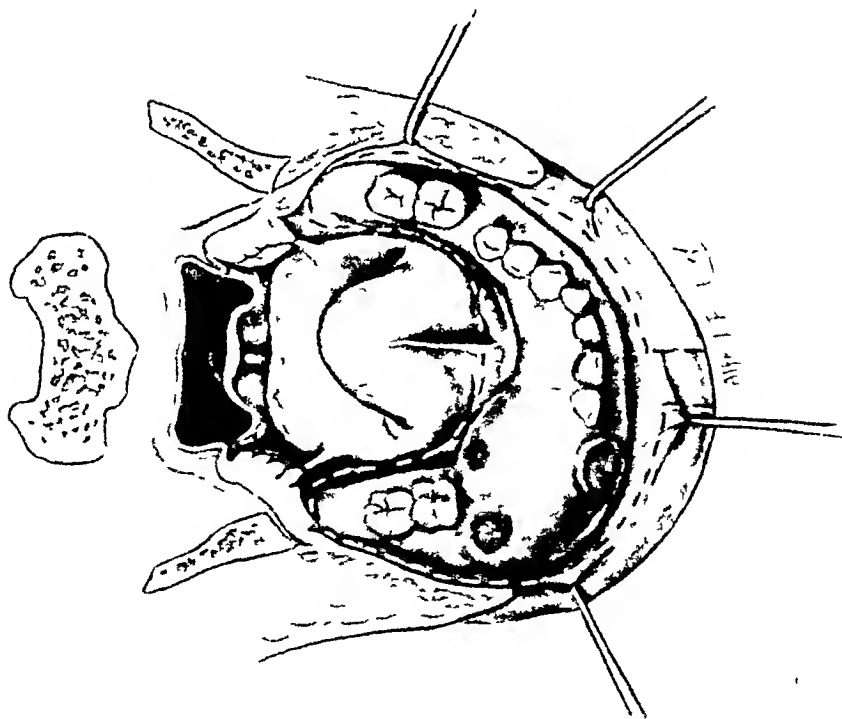


Fig 6—Intra-oral operative incision

The external and intra-oral operative incisions were carefully closed with interrupted vertical mattress sutures of Dermalon, a rubber tube drain was placed in each pterygoid fossa (Fig 8) A pressure dressing was applied The operating time was 4 hours The patient received 1,500 cc of whole blood and 500 cc of 5% dextrose solution during the

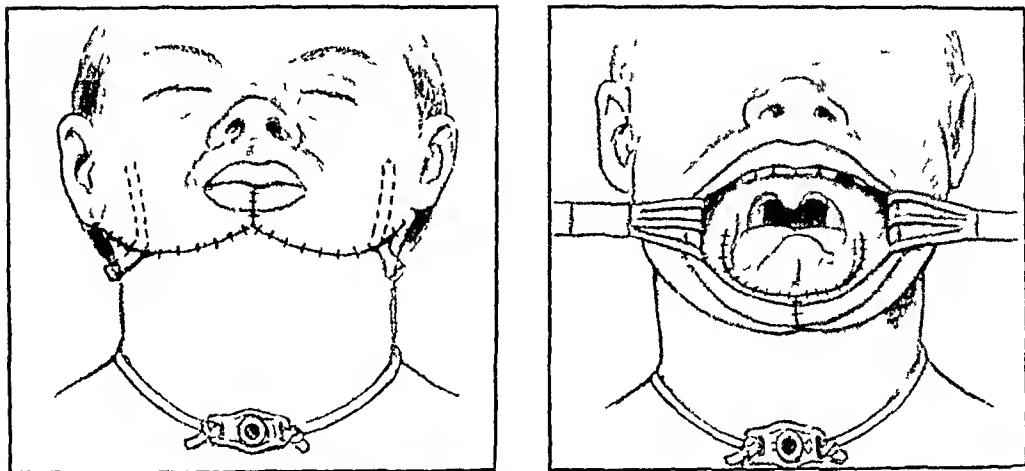


FIG 8—External and intra-oral suture lines



FIG 9



FIG 10

FIG 9—Full face postoperative appearance (December, 1948)

FIG 10—Left lateral postoperative appearance (December, 1948)

procedure Two grams of sodium pentothal were administered The blood pressure, respirations, and pulse remained steady during the operation The patient was returned to the ward in good condition

Pathologic report on the operative specimen was adamantinoma of the mandible with metastasis to a solitary cervical lymph node

Postoperative course The postoperative recovery was uneventful and satisfactory Penicillin (50,000 units every three hours) was given intramuscularly for five days

following which the temperature remained normal. Two 500 cc blood transfusions were given, the first on the fourth and the second on the sixth postoperative day. High caloric, high vitamin, liquid feedings were started on the first postoperative day, the formula was given through a No. 16 urethral catheter which was passed through the nasal cavity into the cervical esophagus. The oral cavity was thoroughly cleaned with a power spray of saline solution twice a day, a gauze pack saturated with a thin solution of zinc peroxide was maintained in the oral cavity along the suture line.

The drains were removed from the pterygoid fossae on the 3rd postoperative day. The tracheostomy tube was corked on the 4th day and removed on the 5th.

The patient started drinking a liquid diet by mouth on the 5th day and was discharged from the hospital on the 10th day. The external and intra-oral wounds were healing by primary union, all skin sutures were removed. However, the patient was partially incontinent of saliva which drooled from his unsupported and edematous lower lip.

During the subsequent five days all sutures were removed from the oral cavity wound, the edema of the lower lip subsided, and the patient ceased to drool. His speech became distinct and he was able to eat a soft diet.

This patient has been examined at regular intervals in our Recall Clinic. His general health remains excellent and there is no further evidence of recurrent or residual tumor. At the time of his last examination on December 15, 1948, he had returned to his regular job as a porter and is self-supporting.

SUMMARY

The surgical management of a 32-year-old Negro with a huge adamantinoma of the mandible and with a metastatic cervical lymph node is discussed. Pictures of the patient and drawings of the operation are presented.

SPONTANEOUS RUPTURE OF THE ESOPHAGUS*

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SPONTANEOUS RUPTURE of the esophagus is sufficiently uncommon to justify the reporting of this case. The frequent difficulty in diagnosis is illustrated by this case and emphasizes the importance of early diagnosis if recovery is to be made in this condition which has had a mortality rate approaching 100 per cent.

CASE REPORT

H G, N Y H No 166320, a 52-year-old white married laborer, was admitted to the New York Hospital for the first time on May 26, 1948, complaining of left chest pain and shortness of breath. The night prior to admission, the patient had consumed an unknown quantity of beer and had retired at midnight. At 4:20 A M he awoke with the desire to defecate and, while straining at stool, he suddenly became nauseated and vomited. The character of the vomitus was not noted. He had the sudden sensation of "something giving way, the stomach went up and never came down", associated with this was a severe pain in his epigastrium and left lower chest and he experienced marked shortness of breath.

Past History Pneumonia at age of 15, "pleurisy" in 1934, following a "cold," without sequelae, in 1944 a chest plate revealed a nodular tuberculous infiltration at the second left interspace apparently stable and repeat chest x-ray two months later revealed no change in this lesion. Patient consumed four or five glasses of beer daily.

Review of system Chronic nasal discharge and chronic non-productive morning cough, epigastric distress and "gas" following meals, relieved by alkali for about one year.

Physical Examination T 37° C, P 130, R 22, BP 180/120. On admission at 5 A M the patient was well developed, moderately obese and in acute distress, slightly cyanotic with grunting respirations. Lungs Slight dullness at left base but otherwise clear. Abdomen distended and tympanitic with resistance and tenderness high in the left upper quadrant.

Laboratory Sp gr 1025, reaction acid, albumin 4 plus, sugar 0, occasional RBC and WBC in sediment. Blood HGB 17 Gm, RBC 7.2 million, WBC 14,800 with 72% polymorphonuclear leucocytes.

A plain film of the abdomen was negative and a chest film revealed the posterior half of the diaphragm to be covered by a layer of fluid on the lateral projection.

Three hours following admission the patient's blood pressure had fallen to 130/110 and the pain became more localized to the left lower chest. A tube was passed into the stomach without difficulty and 1000 cc of fluid and a moderate amount of air was aspirated. A thoracentesis was performed in the left eighth interspace and 850 cc of brownish fluid obtained. Three hundred thousand units of penicillin was introduced into the pleural cavity at this time. The pleural fluid was found to contain 121,000 WBC/mm³ and 5,000 RBC/cmm. A chest plate taken after completion of this procedure disclosed bilateral pleural effusion. Not reported at this time but noted later in reviewing the film was the presence of minimal mediastinal and cervical subcutaneous emphysema. An EKG showed sinus tachycardia and left axis deviation.

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The patient was placed in an oxygen tent and parenteral fluids and large doses of penicillin were administered. His pulse varied from 100 to 140, and his course was febrile, fluctuating from 38 to 38.6° C rectally.

On May 28, 1948, thoracentesis was again performed and 200 cc of dark brown fluid was withdrawn, 300,000 units of penicillin and 0.5 Gm of streptomycin were instilled into the pleural space. The patient was also started on intramuscular streptomycin. Culture of the pleural fluid yielded gamma non-hemolytic streptococci, *B. proteus vulgaris*, *C. welchii* and *E. coli*. The patient took oral fluids in adequate amounts after the third hospital day. He continued to be cyanotic when out of the oxygen tent and appeared acutely ill. Daily thoracentesis was performed with instillation of penicillin and streptomycin. By June 2nd, 1948, cultures of the pleural fluid were overgrown with *Mompha albicans* and roentgenograms of the chest revealed loculated fluid in the left chest with pockets of air.

On June 3, 1948, open drainage of the empyema cavity was performed under local anesthesia, supplemented with sodium pentothal. A large empyema cavity was found, the walls of which were covered with a grayish-green fibrinous slough and communicated with the posterior mediastinum. Drainage was instituted with 6 cigarette drains and 2 soft rubber tubes. Postoperatively streptomycin and penicillin were continued but the patient's course was progressively downhill, with elevation of pulse and temperature. The patient expired on the fifth postoperative day, 13 days after entering the hospital.

At autopsy, a perforation two and a half centimeters in diameter in the posterior portion of the terminal esophagus was found, just above the diaphragm. There was no evidence of ulceration or tumor. The perforation communicated with the posterior mediastinum and left pleural cavity. There was posterior mediastinitis and a left empyema with surgical drainage. The pericardial sac contained 50 cc of cloudy fluid and there was thickening of the visceral and parietal pericardium. Additional findings were those of a chronic gastric ulcer on the lesser curvature 6 cm from the pylorus and a second small acute ulcer in the pylorus. There was bilateral chronic pyelonephritis with minimal hydronephrosis. A calcified tuberculous nodule was found in the left upper lobe.

DISCUSSION

The majority of references to spontaneous rupture of the esophagus in the literature are in the form of case reports. According to Eliason and Welty¹ the first recorded case was that described by the Dutch physician Boerhaave in 1724. Extensive reviews of the subject have been made by Fitz⁷ in 1877, Walker¹³ in 1914 and Klem and Grossman⁹ in 1943, the last named authors being able to find 40 cases in the literature to that date.

Recovery has seldom been recorded, and most authors consider the condition uniformly fatal (Frink,⁶ Eliason and Welty¹), however, survival has occurred in three instances when drainage of the resulting empyema was followed by recovery. Ballin and Salzstein¹ in 1922 described the case of a 15-year-old boy who developed empyema following an episode of severe vomiting. The boy recovered after drainage of the empyema cavity although an esophageal fistula persisted for approximately a year after operation. In an editorial comment in 1944, Graham⁷ stated that he had seen two cases in which drainage of the empyema cavity resulted in healing. Direct attack on the defect in the esophagus has seldom been attempted largely due to the difficulty in making the diagnosis early enough. In 1944 suture of the esophagus following spontaneous rupture was carried out by Collis,³ however, the patient survived only 21 hours after operation. Hertzog and Leighton⁸ in 1946 performed closure

of the esophagus with drainage. The patient expired on the sixth postoperative day from a pulmonary embolus. The first successful closure was reported by Barrett² in 1947. He records the case of a 46-year-old female who developed an episode of sudden vomiting (13 days after hysterectomy) resulting in rupture of the esophagus. Operation was performed 10 hours after perforation, closure was accomplished and drainage instituted with satisfactory recovery.

Although this catastrophe usually occurs in adults after the third decade of life, it has been recorded in childhood. Menne and Moore¹¹ in 1921 submitted the case of a five months old female and cited three others in children aged 4 months, 3 years and 7 years.

ETIOLOGY

An adequate explanation of rupture of the apparently healthy esophagus is still lacking. The earliest investigations were those of Zenker and von Ziemssen¹³ and of McKenzie¹⁰. These workers demonstrated the lower portion of the esophagus was the weakest when distended by water and that pressures of from 5 to 11 lbs. of water were required to cause rupture of the esophagus. Weiss and Mallory¹⁴ studied lesions about the cardiac orifice of the stomach produced by vomiting and at autopsy found fissure-like lesions in the mucosa in patients who had been vomiting persistently. In their analysis, they concluded "that pressure changes in the stomach during the disturbed mechanism of the coordinated motor changes which accompany vomiting and continual regurgitation of gastric juice over the mucosa of the cardia are the most significant changes."

Anatomically, the esophagus is a vertical midline organ, however, in its upper portion it extends slightly to the left of the midline, in the lower portion deviates somewhat to the right and then veers to the left to pass through the esophageal hiatus to join the stomach. The act of vomiting is initiated by a rapid inspiration and closure of the glottis. The pyloric portion of the stomach constricts and the contents of the stomach are forcibly ejected through the relaxed cardiac orifice by contraction of the abdominal wall musculature. Thus, gastric contents are forced suddenly against the weakest portion of the esophagus with considerable force. The investigations of Weiss and Mallory¹⁴ show that fissures in the mucosa about the cardiac orifice are frequently produced without rupture occurring. Vinson¹² reported cases of stricture of the lower esophagus following the pernicious vomiting of pregnancy. The findings indicate that frequently vomiting may produce tears in the mucosa of the esophagus but not involving all layers, and suggests that rupture may occur "spontaneously" in an esophagus that is already weakened by fissures from previous episodes of vomiting.

CLINICAL PICTURE

The patient is usually a middle-aged male from whom a history of frequent intake of alcohol is obtained. The episode usually occurs after ingestion of a quantity of intoxicating drink or a heavy meal. Vomiting is followed by the sudden onset of high epigastric and left lower chest pain and the patient may describe the sensation of tearing associated with the act of vomiting.

On examination the patient appears acutely ill and presents a rapid pulse and lowered blood pressure. Dyspnea is usually present associated with splinting of the chest and grunting respiration. Because rupture of the esophagus is usually followed by the extravasation of gastric contents into the left pleural cavity, signs of a left pleural effusion may rapidly develop. Tenderness in the epigastrium or left upper quadrant are present.

Roentgenograms of the chest show pleural effusion early and this finding is progressive. Significant is the finding of mediastinal emphysema which is easily overlooked. If thoracentesis is performed, the aspirated fluid should be titrated for free acid. Some patients have been given barium by mouth and the defect in the esophagus demonstrated by the extravasation of the barium into the pleural cavity.

TREATMENT

The recent cases of Hertzog⁸ and of Barrett² indicate the importance of early diagnosis with the view of undertaking prompt operation to accomplish closure of the defect. Early measures are thus to be directed toward establishing the diagnosis and preparing the patient for operation. Accordingly, oxygen, sedation, antibiotics and hydration are indicated. There is some question as to whether or not a tube should be passed into the stomach. It would seem that an attempt should be made for if the tube were to enter the pleural space, it would aid in establishing conclusively the diagnosis, however, if the tube were to be passed successfully into the stomach, not only would it aid in decompressing the stomach and help prevent further insult to the pleural cavity by the acid gastric content, but technically it might facilitate the operative procedure by allowing more ready identification of the esophagus at the time of thoracotomy.

At operation Barrett² advises transpleural closure of the defect followed by closed underwater drainage of the pleural space. Cultures of the pleural fluid should aid in the choice of antimicrobial therapy.

SUMMARY AND CONCLUSIONS

A case of spontaneous rupture of the esophagus is presented.

The etiology of the condition is discussed. Investigations and clinical findings suggest that it is the result of direct force of the gastric contents in vomiting upon an esophagus that may have undergone pathologic changes.

Early diagnosis and operation should provide for recovery in this formerly uniformly fatal condition.

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CONGENITAL INTESTINAL ATRESIA*

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CONGENITAL INTESTINAL ATRESIA is an uncommon condition although the true incidence is probably considerably higher than that indicated by the number of cases which have reached the literature. Most cases have not been recorded until recently, and even now many infant deaths due to intestinal atresia remain undiagnosed or are not reported. Until some central Registry for the recording of such cases is set up, it is incumbent upon any physician encountering one to see that at least a brief report is entered in the literature. This is particularly the case in view of the extremely high mortality associated with the malformation, a mortality which early recognition and prompt adequate treatment seems to be lessening appreciably. The case encountered by the authors was that of a complete high jejunal atresia in a three and one-half pound premature infant who recovered following jejuno-jejunostomy, the smallest case on record in which a successful result was achieved. An incomplete rotation of the colon was also present but this was not obstructing and did not therefore influence the clinical picture or appreciably alter the surgical problem.

CASE REPORT

F G, Sydenham Hospital No 108318, was a premature male infant spontaneously delivered on March 12, 1948, after a 30-week gestation (Dr Daniel Wanderman). There had been two previous pregnancies, a full term stillbirth four years before, and a full term forceps delivery of a normal boy two years ago. The mother was Rh negative with no demonstrable antibody formation. No history of virus infection during pregnancy could be elicited.

The infant weighed 3 lbs 14 ozs at birth and was cyanotic but responded to aspiration and oxygen. Physical examination revealed marked overriding of all skull bones at the parietal, sagittal and occipital sutures, with complete closure of the anterior and posterior fontanelles. The eyes were wideset and a cataract-like lesion of the right was noted. The lungs were fully aerated, the heart normal. The abdomen was soft, the liver edge palpable one finger below the costal margin.

The infant was placed in an incubator with continuous oxygen and 5 mg vitamin K daily. Pediatric care was supervised by Dr Lawrence B Slobody. After twelve hours of starvation, small amounts of glucose water were offered for twelve hours followed by a 1:3 evaporated milk formula. On the second day after delivery, regurgitation after feeding began, the milk curds being mixed with thin yellow fluid. Moderate icterus and a petechial rash on the bregma and the dorsum of the feet were noted, and the temperature rose to 102.8 degrees. A small meconium stool was passed. All oral feeding was stopped and intensive parenteral hydration with saline and Hartman's solution was begun. Intramuscular penicillin was also given. Intermittent vomiting continued and by the evening of the third day, the infant appeared markedly dehydrated and in very grave condition. There was no appreciable distention and no peristaltic waves or pyloric tumor were observed.

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On the fourth day, the general condition was somewhat better. The icterus had deepened but the state of hydration had improved. *Regurgitation continued but the infant seemed to retain small amounts of gavage feedings which had been added to the regimen.* Several more meconium stools were passed. The blood count revealed a hemoglobin of 14.5 Gm, a red blood count of 5,020,000 per cu mm, and a white blood count of 24,600 per cu mm with 16 immature forms, 57 mature polymorphonuclear leucocytes, 1 eosinophil, 22 lymphocytes, 4 monocytes and 1 nucleated red blood cell per 100 whites. A slight trace of bile was present in the urine. A plain roentgen film of the abdomen

FG.

3-16-48



FIG 1—March 16, 1948, plain film of abdomen showing stomach, duodenum, and beginning of jejunum (arrow) markedly distended by gas. No gas is seen in remainder of intestine.

(March 16, 1948) revealed a large collection of air in the stomach, duodenum, and proximal few inches of jejunum. No gas was observed in the intestine distal to this (Fig 1).

The appearance and clinical course were suggestive of high intestinal obstruction but because of the absence of abdominal distention or peristaltic waves and the apparent partial retention of gavage feedings and the passage of meconium stools, a thin barium mixture

was given by tube to corroborate the diagnosis. Meanwhile, hydration and supportive therapy were continued. The roentgenogram after barium administration showed passage of the mixture only as far as the first part of the jejunum (Fig 2). The diagnosis of obstruction of the upper jejunum was now clear and efforts were made to prepare the infant for operation. By the following day (March 18, 1948) his condition was sufficiently improved to attempt surgery. The weight on this day was $3\frac{1}{2}$ lbs.

F.G

3-17-48



FIG 2—March 17, 1948, Film after barium showing abrupt termination of barium column at proximal jejunum (arrow)

With a blood transfusion running and a gastric tube indwelling, laparotomy was performed (E E J). The abdomen was opened through a right rectus muscle splitting incision. All the intestines were delivered. The large intestine was found to be incompletely rotated with the cecum subhepatic in location and the ascending and transverse

colon adherent to the transverse mesocolon and posterior peritoneum. These had to be dissected free before the pathologic condition responsible for the obstruction could be appreciated and exposed. After division of the adhesions and liberation of the colon, marked distention of the stomach, duodenum, and first portion of the jejunum was seen. This terminated about an inch beyond the ligament of Treitz in a blind pouch without continuity with the distal jejunum. Though tremendously dilated the bowel was viable. The distal blind jejunal end was located by tracing proximally from the ileocecal valve. The proximal segment of jejunum beyond the ligament of Treitz was too short to permit anastomosis. This technical difficulty was solved by reduction of the proximal segment through the fossa of Treitz, made possible by the blind termination. The distal bowel was so collapsed that its diameter was less than 0.5 cm. Its caliber was enlarged by distending it with saline and a two layer side-to-side jejuno-jejunostomy was then performed. Exploration revealed no further abnormalities. The wound was closed with interrupted figure-of-eight sutures of No. 32 stainless steel wire through fascia and peritoneum. The skin was closed with interrupted silk sutures.

The infant was replaced in the incubator with external heat and continuous oxygen. The gastric tube was left in situ. Penicillin was continued. During the first postoperative day the temperature rose to 102.4 degrees. The infant voided, and regurgitated small amounts of bile-stained fluid. Fluid requirements were met by hypodermoclysis. Twenty hours postoperatively small amounts of a 1:3 evaporated milk formula were fed through the indwelling tube. At this time the red blood count was 2,850,000 per cu mm and the hemoglobin 8.9 Gm. On the second day the baby retained about ½ ounce every 2 hours with occasional regurgitation of bile-stained fluid. Clyses were continued and a blood transfusion given. Twitching motions of the right arm and leg developed but responded to calcium therapy. Thirty-six hours after operation a formed yellow stool was passed which was strongly positive for occult blood, and thereafter about 3 to 4 yellow stools were passed daily. The infant's weight was 4 lbs. 2 ozs. on the seventh postoperative day. He gradually took larger and more concentrated feedings, with infrequent regurgitation. Repeated transfusions were given on the 2nd, 8th, 11th, and 33rd days for recurrent drops in hemoglobin. The icterus meanwhile had diminished so that it was only faintly appreciable.

Five weeks after the operation the infant was taking 2½ ounces of a strong formula. His weight at this time was 5½ lbs. The anterior fontanelle had opened and the sutures also seemed to be separating somewhat. The lesion in the right eye, according to the opinion of an ophthalmologist, was an embryoma. On May 7, 1948, 7 weeks after operation, the infant was discharged from the hospital weighing 6 lbs.

His development since has been progressive and, as far as can be made out, normal. On August 3, 1948 his weight was 10 lbs. 12 ozs. The head was seen to have grown proportionately to the rest of the body. The anterior fontanelle admitted a finger-tip and the skull sutures were palpable. The reflexes and reactions seemed within normal limits for the age. The wound was solidly healed and there were no digestive or bowel disturbances.

DISCUSSION

Atresia of the intestine may occur in the form of an internal diaphragm or, more commonly, the intestine ends as a blind sac discontinuous with the distal bowel or connected only by a fibrous strand. Multiple atresias, while less common, occur. Proximal to the obstruction the bowel is markedly distended, distally, it is very small and contains no gas. The cause is an arrest in development during the second or third month of fetal life when the bowel which has become filled with rapidly proliferating epithelium normally reestablishes its lumen.

The actual incidence of the lesion is difficult to appraise because of incomplete reporting and missed diagnoses. Without attempting to drain the literature, a few references will help to give an impression of the incidence. In 1922 Davis and Poynter collected 401 cases and added one. This figure included 134 atresias of the duodenum and 67 of the colon. Webb and Wangenstein in 1931 estimated the incidence of atresia and stenosis combined as about 1 to 20,000 infants. Including all the intestine below the pylorus and above the rectum, they found about 500 cases reported previously and added 13 cases of atresia and 4 of stenosis. Cohen in 1941 stated that since Webb and Wangenstein's paper at least 150 additional cases had been reported but they included all varieties of intestinal obstruction. In the same year Ladd and Gross reported 52 cases of intestinal atresia, only two of which were in the colon. Since 1941 individual cases or small series have been added by Duckett, by Glover, Smith and Eitzen, by Impink and Clammer, by Stock and Cannon, by Miller, Green-gård, Raycraft and McFadden, by Erb and Smith, by Arnheim, by Biggs and Pontius, by Darne, by Judd, and others.

Symptoms usually begin on the first day of life. Vomiting is the presenting symptom. Persistent vomiting leads rapidly to severe dehydration. The vomitus almost always contains bile. The character of the vomitus will of course depend upon the level of the obstruction. While the stools may resemble normal meconium they are usually smaller and dryer. Farber's test which demonstrates the presence or absence of vermiform cells in a stool specimen is of great usefulness in determining whether a complete obstruction exists. Abdominal distention may be present if the obstruction is low but may be difficult to evaluate if the atresia is high. Peristaltic waves crossing the abdomen may be seen but these are not constant.

A plain roentgenogram of the abdomen can give considerable information. No air is present in the intestine distal to the site of obstruction and if this be high, a dilated air-filled stomach, duodenum and upper jejunum with no air in the lower part of the field may establish the diagnosis. With ileal obstruction, multiple dilated loops with fluid levels are seen which are characteristic of intestinal obstruction but not necessarily of ileal atresia. Barium may be given to aid in the roentgen diagnosis but the danger of aspirating vomited barium accompanies such a procedure.

Surgical relief of the obstruction offers the only hope for survival. Otherwise, the markedly distended proximal blind loop undergoes necrosis, and perforation with peritonitis supervene. The procedure of choice is a side-tracking anastomosis. Naturally, resection of any nonviable bowel must be performed. Enterostomy should not be done as it always results in death due to rapid dehydration. Technically the operation presents certain difficulties due to the friability and distention of the proximal loop and the extreme narrow caliber of the distal. An excellent description of the technic may be found in Ladd and Gross.

Of equal importance to the operation is of course the pre- and postoperative handling of the infant. Fluid balance must be maintained and this is not an easy

procedure since it entails the administration of parenteral fluid several times a day. Blood and other supportive therapy must be utilized as indicated. A gastric tube should be introduced before the operation and should be continued after operation for as long as necessary. Operation should not be performed until the general condition has been brought to its best possible level even if this involves some delay. The infant frequently is not able to take feedings for several days after surgery and the stomach should be kept empty as long as vomiting persists. Feedings must be started carefully and increased judiciously. In all, the immediate period of postoperative care is one which requires painstaking and meticulous attention.

The mortality without operation is 100 per cent. According to Davis and Poynter, without operation death occurs after an average of 5 days when the obstruction is at the duodenal level as compared to 8 days at the colonic level. Even with surgery the mortality is quite high although it has lessened appreciably with modern techniques and improved preparation and postoperative care. The first recovery is credited to Fockens in 1911 who established a side-to-side anastomosis seven days after birth in a case of atresia at the junction of the middle and lower thirds of the small intestine. Of the 500 cases collected by Webb and Wangenstein only 10 recovered following surgery although the number operated upon is not given. Seven of Ladd and Gross' series of 52 cases treated surgically recovered. In Arnheim's report in 1945 he states that only 11 cases treated surgically to that date survived the procedure. While a number of individual successes have been added since then it is apparent that the mortality is still quite high.

The case reported here is of particular interest because it illustrates that even in a three and one-half pound premature infant a successful result may be achieved. The clinical picture and roentgen findings were typical of high jejunal atresia. The picture was complicated by the presence of icterus and other congenital defects were present in the form of closed fontanelles, an embryoma of the right eye, and an incompletely rotated colon. The last was not obstructing but required liberation and reduction before the primary pathology could be exposed and jejuno-jejunostomy performed.

SUMMARY

1. A case of jejunal atresia in a three and one-half pound premature infant successfully treated by jejuno-jejunostomy, is presented.
2. Congenital intestinal atresia is briefly reviewed.

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MULTIPLE LIPOMAS OF THE STOMACH AND DUODENUM*

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LESS THAN 2 per cent of all surgically treated gastric tumors are benign, and among these about 3 per cent are lipomas. The incidence of benign tumors of the duodenum is considerably lower. In either region they may appear within the wall or as polypoid lesions. The symptoms are dependent on their location, size and character. A high percentage of benign tumors is symptomless and discovered only at autopsy. Not infrequently, however, the mucous membrane over a benign tumor ulcerates and produces symptoms of peptic ulcer, *i e*, pain and/or gastro-intestinal bleeding. Hemorrhage is sometimes massive. A benign tumor near the pylorus or in close relationship to the ampulla of Vater may produce symptoms of obstruction at these points. A pedunculated tumor, especially in the duodenum, may cause intermittent partial intussusception for the same reason that polyps of the jejunum and ileum may do so.

The case of a patient with an intramural lipoma of the stomach and intramural and polypoid lipomas of the duodenum is reported. The patient presented symptoms of hemorrhage and also intermittent episodes of pain.

M B S, a white male, age 36, was admitted to St Francis Hospital March 30, 1948, because of recent gastro-intestinal hemorrhage. On admission gross bleeding had ceased and he was not feeling ill. His chief complaints on admission were (1) Three episodes of tarry stools experienced in the past two years, accompanied by severe fatigue. The last episode occurred one week before admission to the hospital and was accompanied by faintness, palpitation and dyspnea. (2) Several episodes of vague abdominal discomfort accompanied by nausea during the past four years. He had consulted several different physicians for these attacks and the diagnosis was generally that of "probable appendicitis." However, the findings had never been definite enough to warrant surgical intervention.

The patient stated that the attacks of pain did not occur at the time of the tarry stools. Past and family history were irrelevant except that one child had been treated surgically for a Wilm's tumor.

Physical examination revealed a well developed, well nourished white male, apparently not acutely ill. General examination was negative throughout except for very slight tenderness to deep pressure just above the umbilicus. Laboratory studies including urinalysis, blood count, Kahn, blood sugar, NPN, serum amylase, and sedimentation rate were all non-contributory except that occult blood was present in the stool.

Roentgen-Ray Studies. A summary of the two examinations made showed a large filling defect in the stomach apparently projecting into the lumen although nothing could be palpated at the time of examination. The pylorus was not obstructed and the duodenal cap filled normally. Just distal to the cap was another large irregular deformity around

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which the barium seemed to flow, although again nothing could be palpated at the time. The stomach emptied normally in 5 hours.

On the basis of the roentgenologic findings the diagnosis rested between aberrant pancreatic tissue, a pancreatic tumor with secondary deformity of the stomach or the reverse. Other possibilities included leiomyomata, lipomata, and primary retroperitoneal growths such as Hodgkin's disease, or lymphosarcoma. Our final diagnosis was multiple tumors of undetermined type. Because of the patient's history of hemorrhage surgical exploration was advised.



FIG 1 —The antrum is contracting. The bulb is filled and the large irregular filling defect in the duodenal loop is visualized.

On April 2, 1948, the abdomen was explored through an upper transverse incision. Examination disclosed a large, soft, flat non-pedunculated tumor in the posterior wall of the stomach in the pre-pyloric region. A similar type of tumor occurred within the anterior wall of the second part of the duodenum, and upon opening the duodenum, it was apparent that a third tumor, which was pedunculated and arose from the mucosa at the lower border of the intramural tumor, projected down into the lumen of the third part of the duodenum.

Further exploration of the abdomen revealed no abnormal glands or other pathology. A subtotal gastrectomy and a resection of the anterior (tumor bearing) wall of the second portion of the duodenum was accomplished, re-establishing gastro-intestinal continuity by a retro-colic, Polya type, of gastro-jejunostomy.

Pathologic Examination. **Stomach.** Gross. The specimen consisted of the distal portion of the stomach and measured 13 cms along the greater curvature. It had a max-

imum circumference of 16 cms. A thick, soft, intramural tumor, 9 x 8 x 3.5 cm in dimensions, was palpable on the posterior wall. The overlying mucous membrane was smooth and contrasted strikingly with the prominent, greyish-red, rugal folds elsewhere (Fig 2 upper specimen). The cut surface of the tumor revealed lobulated and bright yellow fat which was mainly submucosal in distribution. Microscopic examination showed that the tumor was composed mainly of mature fat cells. Focal congestion, fibrosis and round cells were scattered throughout.

Duodenum Gross pathologic specimen consisted of the anterior portion of the wall of the second part of the duodenum and measured 5 x 3 cm in surface area. A thick, soft, intramural tumor measuring 4 x 3.5 x 1.7 cm was palpated. A similar polypoid tumor covered by ulcerated and purplish red congested mucous membrane projected from the mucous membrane surface of the main specimen. The polyp projected into the lumen towards the third part of the duodenum. The polyp measured 7 cm in length and 3 x 3 cm

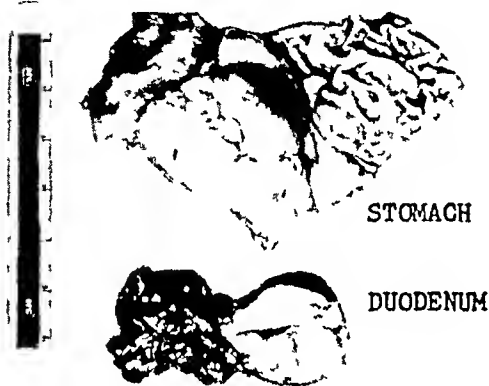


FIG 2—Cut surfaces showing lobulated fatty character of the intramural tumors

in cross section. Two stellate shaped ulcers were apparent in the midportion of the polyp. The largest ulcer measured 1.5 x 2.2 cm in area (Fig 2 lower specimen). The cut surface of the tumor was lobulated and bright yellow, similar to that described in the stomach. Microscopic examination showed moderate congestion and hemorrhage of the mucous membrane over the polypoid lesion. The base of the ulcer described grossly was composed of proliferating and congested capillaries, fibroblasts and scattered polymorphs.

Pathologic diagnosis Lipomas, stomach and duodenum, polypoid in the latter region and associated with secondary ulceration.

Postoperative course was uneventful and he was discharged on April 20, 1948.

DISCUSSION

The preoperative diagnosis of these lesions, if made, is usually made by the roentgenologist. However, in the roentgen diagnosis of benign lesions of the stomach or duodenum it is difficult to determine with any degree of accuracy the histologic nature of the growth. Since these tumors are so unusual, no one has acquired a very extensive experience with them.

However, there are features which aid in the differentiation between benign growths and ulcers or malignant deformity. Most of these tumors grow into the lumen so that they tend to produce a smooth rounded filling defect. Since they are not invasive, the borders, in general, are well demarcated but with obliteration of mucosal pattern. The peristalsis is not greatly affected, if at all. Therefore, emptying time is not influenced unless there is obstruction and, consequently, little or no change in the size of the stomach or duodenum is noted. The growth will move with the stomach on palpation during fluoroscopy and the stomach or duodenum will not be displaced as would be the case with extrinsic masses. Lipomas seem particularly prone to ulcerate so that one may be able to locate a crater, especially on second examination or with the "advantage of hindsight."

SUMMARY

A case of multiple lipomas of stomach and duodenum is presented in a 36-year-old white male. The tumors in the duodenum were in part polypoid and complicated by ulceration of the overlying mucosa. His symptoms were Gastro-intestinal bleeding and episodes of pain. Subtotal gastrectomy and duodenectomy and retro-colic, Polya type, gastro-jejunostomy were performed. The postoperative course was uneventful.

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ANOMALOUS INSERTION OF THE RIGHT HEPATIC DUCT INTO THE CYSTIC DUCT*

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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ANOMALIES OF THE BILIARY DUCT SYSTEM are not infrequent and are of vast importance in adequate assessment of the technic of cholecystectomy Kehr¹ in pointing out the high incidence of morbidity and mortality entailed early in his series observed that, in the majority of cases, this could be directly traced to anomalies in the biliary duct or vascular system Eisendrath² similarly emphasized the necessity of adequate knowledge of the anomalies that might be encountered in the course of what might otherwise be routine cholecystectomy In more recent years Graham *et al*³ and Daseler *et al*⁴ have also served warning of the variations that might be found in dissection of the cholecysto-duodenal ligament, and it is now common knowledge that anomalies must be constantly watched for in the performance of surgery in this region of the body

Recently during a cholecystectomy performed by one of us (RBB) an unusual anomaly was encountered, the right hepatic duct draining into the cystic duct (Fig 1) Because of the reputed rarity of this anatomic condition and its surgical hazard if not recognized, it is deemed timely to report this case

CASE REPORT

The patient, a 42-year-old white male was admitted to Michael Reese Hospital with a typical history and diagnostic findings of gallbladder disease A cholecystectomy was therefore performed, and dissection of the cholecysto-duodenal ligament conducted in the usual manner previously described by this clinic⁵ What were thought to be the hepatic, cystic and common ducts were carefully identified and these along with the vascular structures dissected free At this time, on close observation, it was noted that the duct system was anomalous, the right hepatic duct draining into the cystic immediately below the gallbladder As a result it was necessary to clamp the cystic duct above the union with the right hepatic in order that the right hepatic might drain freely into the common duct Cholecystectomy was then performed from below upward, and the patient's postoperative course was uncomplicated

DISCUSSION

Anomalous insertion of the right hepatic duct into the cystic, or of the cystic into the right hepatic has been observed in both animals and man Boyden⁶ in the course of thousands of dissections of domestic animals noted this condition in a number of instances as indicated by his anatomic drawings Similarly Thompson⁷ and Daseler *et al*⁴ observed examples of this condition in the dissection of cadaver material

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INSERTION OF RIGHT HEPATIC DUCT

Embryologically it would seem that this phenomenon could best be explained by variation in growth of the hepatic diverticulum in its formation of the biliary duct system. This outgrowth of the foregut in its primary division forms the common duct, and the branchings therefrom the cystic duct and gall-bladder, and the hepatic duct. The germination of the hepatic duct then branches to form the right and left hepatic duct system in its secondary ramification.

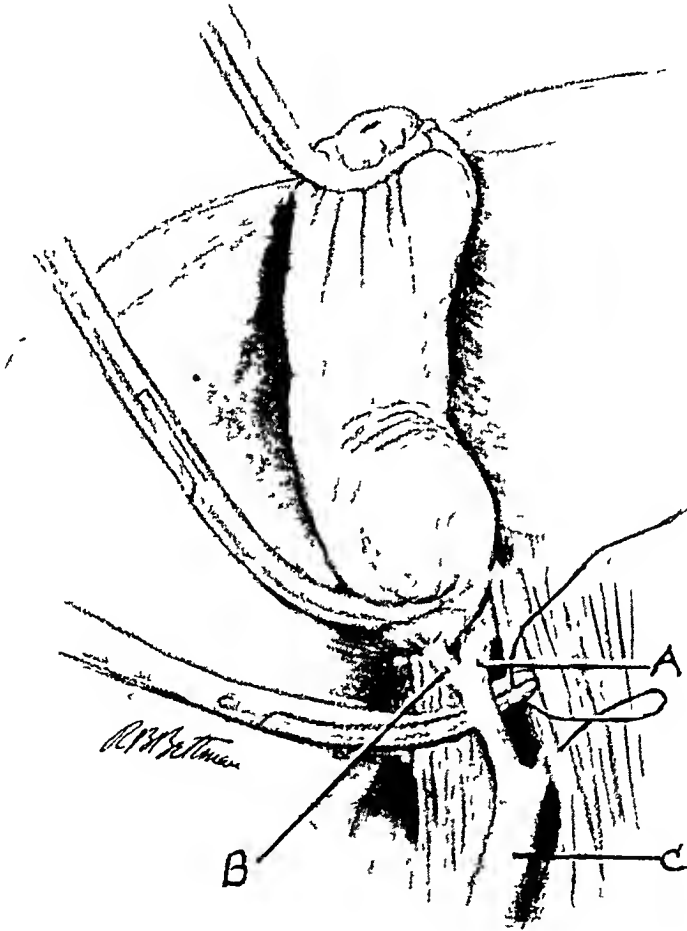


FIG 1—Illustrating the anomalous insertion of the right hepatic into the cystic duct, and how this duct might inadvertently be ligated (a) Right hepatic duct (b) Cystic duct (c) Common duct

fications. An anomaly of the right hepatic entering the cystic could thus occur if an abnormality of the cystic duct bud extended into the liver substance. At the same time it would be necessary that the primary hepatic diverticulum failed to divide, and thus only formed the left hepatic duct.

Another possible explanation of the derivation of this anomalous situation could be found in unusual absorption of the many small secondary branchings

which project from the various buddings of the hepatic diverticulum Leiter⁸ has suggested the additional possibility of an early branching of the primary duodenal bud into right, left and cystic ducts, with the cystic originating so far down as to arise from the right hepatic duct

From the studies of Thompson,⁷ Daseler *et al*⁴ and from those^{2, 9 16} in which this anomaly was not found, it is possible to obtain a reasonable estimate of the incidence of the finding. These results as tabulated (Table I) show that in the course of 1371 cadaver dissections of the biliary tract, anomalous right hepatic-cystic duct union has been encountered only four times.

If one were to judge the relative importance of the problem by the above data it would not be a cause of great concern to any individual operator. However in view of the great number of cholecystectomies performed each year it

TABLE I—*The Incidence of Right Hepatic-Cystic Duct Union Encountered in Cadaver Dissections*

Author	Year	Number of Dissections	Number of Times Anomaly Found
Brewer	1900	100	0
Ruge	1908	50	0
Descomps and De Lalaubie	1910	50	0
Piquand	1910	40	0
Eisendrath	1920	100	0
Flint	1923	200	0
Beaver	1929	57	0
Thompson	1933	50	1
Lurje	1937	194	0
Osler	1945	30	0
Daseler <i>et al</i>	1947	500	3
Total		1371	4

would seem that this surgical anomaly calls for greater awareness on the part of the general population of physicians. That the calculated low incidence of 0.29 percent might be small may be concluded from the series of Daseler *et al*, the most recent of the dissections, where three instances of this anomaly were found in 500 cases. Also in the prior dissection of Thompson one case was revealed in fifty examinations.

Strangely in the course of surgery the condition has not been reported frequently. Considering the expected incidence based on anatomic dissections the fact that only two cases could be discovered in a reasonably complete search of the literature would seemingly imply that either surgical dissections have been incomplete, or that the postoperative complications resulting from the anomaly were not sufficient to warrant further search for their causes.

In Kehr's case¹ calculi lying in the right hepatic duct were thought to be in a diverticulum of the cystic duct. As a result, the hepatic duct was divided and had to be anastomosed to the common duct. In Leiter's case⁸ it was necessary to divide the hepatic ducts in order to remove a tumor of the ducts. The anomaly was observed in the course of the dissection. In this case the hepatic ducts were anastomosed separately to the duodenum. Both these patients did

well postoperatively. In the present instance anastomosis of the duct was not necessary, the cystic duct having been tied off carefully above the junction with the hepatic.

Insofar as complications might be expected, it would seem that two would be probable. These would stem either from obstructing the flow of the right hepatic duct by ligature (Fig 1), or by failing to recognize the situation and leaving a draining right hepatic duct after removing the cystic duct along with a portion of the right hepatic.

From the fact that autopsy reports have not noted the finding of these complications, it would appear that either the anomaly has been recognized, the complications corrected, or else that by themselves, these complications need not prove fatal. This would seem to be a feasible explanation in experimental situations where the right hepatic duct was ligated. In some of the animals so treated it has been observed that collateral channels will shortly allow bile to flow from the right lobe of the liver through the left hepatic duct. Fortunately the reserve of the liver is great and the left lobe apparently is capable of adequately handling the increased load. Clinically, though, there could be little doubt but that in such instances the general status of patients would be poorer over the immediate postoperative period.

In those instances where the right hepatic duct has been severed, the possibility of biliary fistula, or bile peritonitis, would be of greater import. However, bile flow from the severed duct renders this condition relatively easy of recognition.

Treatment of the complications depends on immediate cognizance of the anomaly with prompt repair of the damaged duct. It is, however, appropriate to emphasize that the most important aspect of therapy lies in the field of prevention. Here the prime factors are recognition of the fact that anomalies are not infrequent in large series of cases, and that a knowledge of these is essential. If the morbidity and mortality of cholecystectomy is to be lowered, continued vigil is necessary at the operating table in order to recognize anomalies existing in the hepatic pedicle.

SUMMARY

A case of a rare anomaly of the biliary duct system has been reported. In this instance the right hepatic duct joined the cystic duct just below its emergence from the gallbladder. The cystic duct eventually united with the left hepatic to form the common duct. The literature bearing on the subject has been reviewed and the embryology, incidence, complications and treatment discussed.

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PRIMARY INFLAMMATION OF THE APPENDICES EPIPLOICAE*

WITH REVIEW OF THE LITERATURE AND REPORT
OF SIX ADDITIONAL CASES

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SINCE THE FIRST DESCRIPTION of appendices epiploicae some 400 years ago interest in them as sites of primary disease has recurred from time to time. Scattered individual cases have been reported in which they have been found free in the peritoneal cavity or in which some primary pathologic process has caused surgical intervention. Interest has been stimulated by the excellent reviews of Hunt,¹ Klingenstein,² Fiske³ and more recently by Pines,⁴ but recognition of primary disease of the appendices epiploicae is still rare.

Primary disease of the appendices epiploicae has attracted attention only by its rarity and this continues to be true in spite of the fact that it occurs more frequently than is implied by the infrequency of reports. We feel that it is timely to call attention to primary disease of the appendix epiploica and to present a review of the available literature, bringing the cases up to date and to add six additional cases. In this report we have gathered, and are presenting, only cases in which primary disease of the appendix epiploica have produced acute symptoms and signs which have warranted surgical exploration.

ANATOMY AND PHYSIOLOGY

The anatomy and function of appendices epiploicae should be mentioned. They have been shown to be present as early as the fifth fetal month. They occur along the large bowel except in the region of the rectum, and may have one to three rows though only one or two are usually demonstrated. They are definite fat tabs of irregular shape which are continuous with the subserosal fat layer and are enveloped by a layer of the visceral peritoneum from the large bowel. Their blood supply is gained from one artery and vein from either the superior or inferior mesenteric vessels.

The significance of these structures is obscure and their physiologic function has never been proven but the idea that they play a role in the absorption of fluids and as a protective mechanism for the colon seems justified. This latter may be in protection from other inflammatory processes or from adjacent viscera during peristalsis. Pines⁴ felt that appendices epiploicae acted as protective fat pockets for the redundant intestinal vessels and that this protective mechanism was obviously necessary to prevent collapse and occlusion of the vessels when the bowel became distended. It should be further added that in all probability they have a definite role in the storage of fat.

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PATHOLOGY

The etiology of primary disease within the appendices epiploicae has been discussed by many correspondents ^{2, 3, 5, 6, 7} The consensus of opinions is that torsion of the pedicle is usually the direct cause in spite of the fact that in many cases it cannot be demonstrated It seems reasonable that it is the principal cause of interference of the blood supply, and is due to a variety of conditions, such as movement in adjacent coils of small bowel during vigorous peristalsis and the association of a large appendix epiploica with a long pedicle Infarction may be present and has suggested, when torsion was not demonstrated, that it is due to thrombosis or embolism ^{4, 5} Payr⁸ thought that engorgement could be due to an abnormally long vein becoming twisted about the artery Secondary changes which may occur include simple necrosis, various degenerative processes and gangrene Why they should be the site of a primary inflammatory process has never been explained, though it is obvious when associated with other inflammatory lesions within the abdomen Black⁹ was the first to suggest that they could be the site for developing lipomas

ANALYSIS OF CASES PREVIOUSLY REPORTED

Fifty-eight cases have been previously reviewed or reported in the literature in which the symptoms and signs were of an acute or subacute abdominal disease and subsequently required surgery This does not include cases which appeared to have had a chronic course over months or years, cases in which the appendices epiploicae were found in hernial sacs, noted at autopsy, cases associated with other inflammatory processes, or cases in which they were found incidentally at surgery for some other disease

The site of the diseased appendix epiploica was on the sigmoid colon in 28 cases and on the cecum in 13 cases The others occurred on various parts of the remaining colon Torsion of the appendix epiploica was the most frequent diagnosis given, though in a majority of the cases the findings were not described Thirty-six of the cases occurred in males and 22 in females The ages ranged from 18 to 76 years with a majority (31 cases) occurring between 30 and 50 years The symptoms and signs were incomplete in many cases, however, all cases had pain and it appears to be the only constant finding In 46 cases tenderness was present and was most commonly seen overlying the diseased appendage Nausea, vomiting or both occurred about as frequently as rigidity, that is, in about one-half of the cases Rebound tenderness and a mass were only occasional findings

REPORT OF ADDITIONAL CASES

Case 1—A 40-year-old white male was admitted to the hospital with a history of gradual onset of lower abdominal pain 48 hours before which increased in severity and moved to right lower quadrant 24 hours prior to admission He had a constant desire to defecate after onset No nausea or vomiting was associated He had had a previous similar attack 13 years ago lasting 24 hours Examination revealed temperature of 98.6, WBC was 7,050 He exhibited moderate tenderness and well marked rigidity in right lower quadrant with no rebound tenderness Preoperative diagnosis of acute appendicitis was made At operation a large amount of bloody fluid was found and a gangrenous

appendix epiploica of the sigmoid measuring 6 x 4 cm was present and removed. Post-operative course was uneventful.

Case 2—A 47-year-old female was admitted to the hospital with a history of sudden gripping pain in the midline, above the symphysis for 12 hours previously. The pain "went through to the back." She had anorexia, but no nausea or vomiting. The pain moved to the lower left quadrant, back to midline and then to right lower quadrant. There was an urge to defecate with results. Examination revealed moderate tenderness over right lower quadrant with rebound tenderness to the same side. This tenderness shifted with position of the patient, from right lower quadrant to midline to left lower quadrant and back to right lower quadrant. Pelvic examination revealed tenderness in the right cul-de-sac. The temperature was 99.4, WBC 11,700. Preoperative diagnosis was acute appendicitis. At operation there was found a swollen blue appendix epiploica attached to the sigmoid, which was removed. Postoperative course was uneventful.

Case 3—A 32-year-old female was admitted to the hospital with a history of fullness and discomfort in abdomen for 48 hours becoming painful and moving to right lower quadrant. This was not relieved by enemas or rest in bed as previous attacks had been. There was no nausea or vomiting. Moderately severe pain in right lower quadrant persisted. Examination revealed the temperature to be 99.0 and WBC 12,400. Moderate tenderness in right lower quadrant was present with no rebound tenderness and no masses. Preoperative diagnosis was acute appendicitis. At operation a blue gangrenous appendage was found in the pelvis which was attached to the sigmoid. It was removed and the postoperative course uneventful.

Case 4—A 19-year-old white female entered the hospital for change of cast and further treatment for old fracture of right femur. While in the hospital she had onset of severe cramping abdominal pain which was followed by nausea and vomiting. Pain became more intense and was localized in the right lower quadrant with marked tenderness in same area. Temperature was 99.6 and WBC 14,100. Preoperative diagnosis was acute appendicitis. At operation the appendix was found to be normal and attached to cecum was an enlarged gangrenous appendix epiploica which was removed. The post-operative course was uneventful.

Case 5—A 44-year-old male was admitted to the hospital with a history of slight epigastric pain and dysphagia of 72 hours duration, followed by severe right lower quadrant pain associated with nausea and vomiting. Examination revealed marked tenderness in the right lower quadrant. No masses were felt. The temperature was 100 and WBC 12,500. Preoperative diagnosis was acute appendicitis. At operation a dark gangrenous appendix epiploica measuring 5 x 0.8 cm attached to the cecum was found. It was removed and postoperative course was uneventful.

Case 6—A 34-year-old male was admitted to the hospital with a history of onset of abdominal pain 24 hours previously which had moved to the right lower quadrant and was noticed more when moving about. No nausea or vomiting was associated. He was admitted for a stat appendectomy. Examination revealed temperature of 98.6 and WBC 12,900. Marked tenderness in right lower quadrant was present with rebound tenderness. No masses were palpable. Preoperative diagnosis was acute appendicitis. At operation there was found an enlarged gangrenous appendix epiploica attached to the lower ascending colon. It was removed and postoperative course was uneventful.

DISCUSSION

In Baylor Hospital during the last 10-year period there have been six cases of primary disease of the appendices epiploicae producing symptoms sufficient

to cause surgical exploration. Within this same period of time it is of interest that surgery was done in 2766 cases for acute appendicitis. Also during this period primary disease of an appendix epiploica was found at time of surgery for some other disease process in four instances, yet no history could be obtained of any symptoms which they might have produced.

In the cases we are reporting symptoms were present for 48 hours or less except in one case of 72 hours duration. In four cases onset of pain was localized to the right lower quadrant. In others it was generalized or in the lower abdomen. Nausea and vomiting was present in three cases. In all cases tenderness was moderate to marked and localized to the right lower quadrant. Of considerable interest was the one case in which the tenderness was shifting in character. Rigidity and rebound tenderness was present in three cases each. Low grade temperature elevation was noted in three cases and an elevated WBC count was present in all except one. Torsion was not demonstrated in any of these cases.

We feel that we are justified in only presenting cases associated with symptoms of acute disease and which have required surgical intervention. Though torsion of the pedicle of the appendix epiploica is apparently the most likely cause of disorder, we were unable to show it in any of these cases. We feel that the sign of shifting tenderness should cause one to suspect the condition and want to stress again that in any acute surgical abdomen in which primary disease cannot be demonstrated elsewhere one should explore thoroughly for the presence of a diseased appendix epiploica.

It is quite apparent that pathologic changes may occur in the appendices epiploicae without producing symptoms and this most likely accounts for those found incidentally at other operations and at autopsy. It is just as apparent that in many instances these do produce symptoms and signs of an acute abdominal disease and in such cases surgical exploration is indicated.

SUMMARY

The available literature has been reviewed and the cases of primary disease of the appendix epiploica unassociated with other conditions or which were found incidentally, have been collected and brought up to date. To this number we are adding six cases in which the primary disease justified surgery. We have suggested that shifting tenderness should cause one to suspect the disease, and in all cases of acute abdomens in which a primary disease is not found one should look for a diseased appendix epiploica.

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ANGIOSARCOMA OF THE COLON*†

WITH CASE REPORT

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AND

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THE RARITY OF SARCOMA of the colon is stressed in every treatise on this subject. This condition was first described by A. Debruner¹ in 1883, prior to which time it is likely that it was not recognized by the pathologists as a distinct disease entity. Subsequently additional cases were reported by Jopson and White,² Farl³ and others,^{4, 5, 6, 7, 8} but in a rather careful review of the literature, we have been able to find less than 400 proven cases. Furthermore, of these cases, approximately 95 per cent are lymphosarcomas. In view of the rarity of all types of sarcoma of the colon, we feel that a case report of an angiosarcoma would be of value, particularly since we are unable to find any description of such a neoplasm in the literature.

Although an adequate description of nearly all types of sarcoma of the colon is readily available through numerous sources, very little has been written about angiosarcomas arising in any part of the body, and as stated above, no previous description is obtainable of an angiosarcoma of the colon. However, it is felt that this lesion is an extremely vascular neoplasm which arises from the cells of the outer coat of a blood vessel and it is not considered to be a very highly malignant tumor. A further description of this lesion is incorporated in the following case report.

CASE REPORT

Mrs. H. F., a 46-year-old white female, was admitted to the Bryn Mawr Hospital on November 27, 1945, with a chief complaint of abdominal pain of three days duration. She had apparently been perfectly well until November 24th, at which time she developed a colicky type pain in the left lower quadrant of her abdomen several hours after taking a laxative. Later in the day, the pain increased in severity and was not relieved by an enema. On the following morning she became nauseated, vomited several times and noticed that her abdomen was becoming distended. Further laxatives and enemas during the next 48 hours were ineffectual, at the end of which time her abdomen was considerably distended and the patient was obviously quite ill. She was then admitted to the Bryn Mawr Hospital for further observation.

The past medical history in this case was essentially negative, there having been no serious illnesses or operations. There had been no weight loss and no symptoms referable to her gastro-intestinal tract. Her menstrual history was likewise negative.

Physical examination revealed a rather pale, somewhat obese, white female. Blood pressure was 130/80, temperature 99.2°F, pulse 88, respirations 22. No abnormalities except the following: rather marked distention of the abdomen with considerable tender-

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ANGIOSARCOMA OF COLON

ness in the left lower quadrant, an ill defined boggy mass was palpable at this point. Peristalsis was hypo-active. Rectal examination was negative.

Roentgenologic examination by means of an erect scout film showed the large bowel to be moderately distended proximal to the sigmoid colon.

Immediate treatment consisted of the administration of parenteral fluids and the passage of a Miller-Abbott tube, as a result of which the patient's condition improved quickly and the abdominal distention was relieved in 48 hours. A barium enema thereafter revealed a partial obstruction at the junction of the descending and sigmoid colons. The Miller-Abbott tube was removed and the patient was placed on a

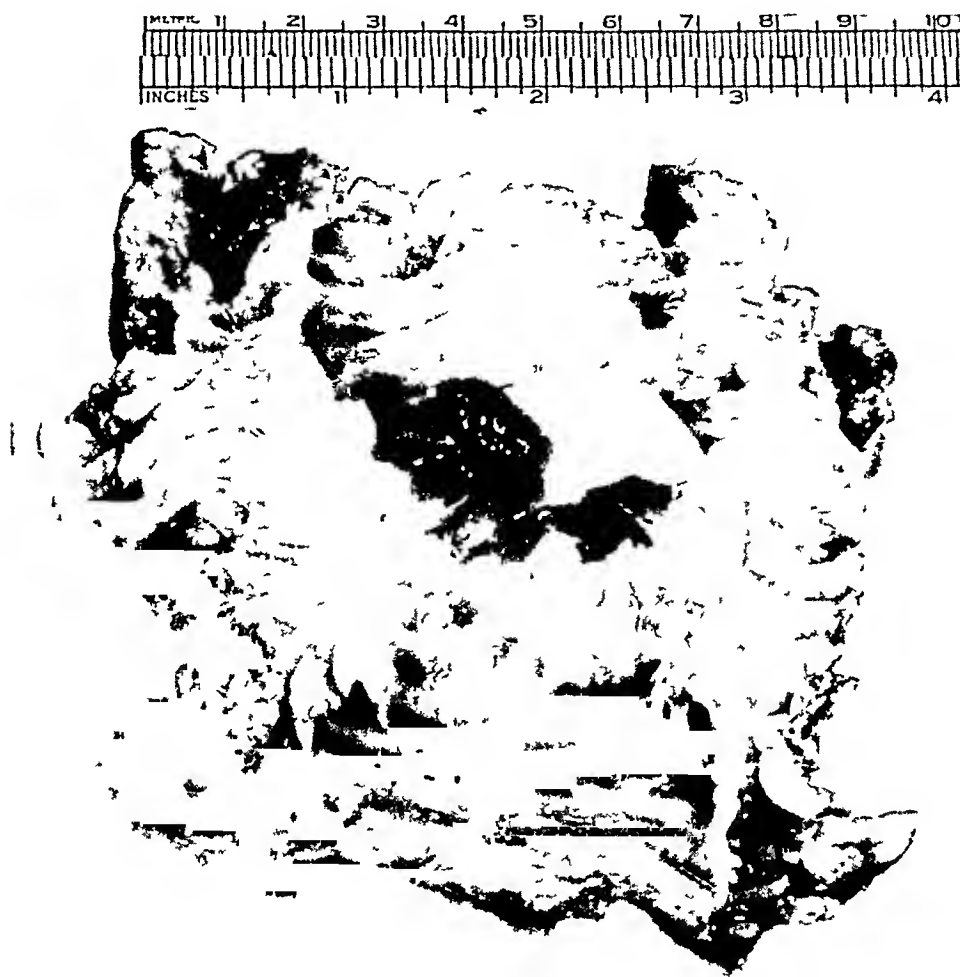


FIG 1—Gross specimen angiosarcoma of sigmoid colon

regimen of sulfasuxidine, parenteral feedings of glucose, saline and blood plasma together with a low residue, high protein diet. Operation was performed on December 5, 1945, eight days following admission.

Operation With continuous procaine spinal anesthesia, the abdomen was opened through a left lower paramedian incision and exploration revealed a firm nodular type growth in the wall of the sigmoid. The serosa of the involved area of bowel was smooth and glistening in appearance. No enlarged lymph nodes were palpable in the mesocolon nor in the retroperitoneal tissues and no gross invasion of surrounding

structures was noted. Similarly, no evidence of metastasis to the liver was present. No abnormalities of the pelvic organs could be detected. Resection of approximately 10 cm of the sigmoid colon together with a large wedge shaped piece of mesocolon was performed, followed by an open end-to-end anastomosis. Five grams of sulfamidate crystals were placed in the abdominal cavity following which the incision was closed in layers without drainage. A tentative diagnosis of carcinoma of the colon was made. Five hundred cubic centimeters of whole blood were administered during operation and the patient's immediate postoperative condition was good.

Postoperative Course Continuous nasal suction with the use of a Levin tube was carried out for the first two postoperative days together with parenteral feedings of glucose in saline and blood plasma. Ambulation was instituted on the first postoperative day. Oral feedings were begun on the third day and at the end of ten days the patient was eating a full high protein, low residue diet and was having regular bowel movements without laxatives. Her incision healed by primary intention and she was discharged from the hospital on December 20, her 15th postoperative day.

Pathologic Report of Specimen (By Dr. Max M. Strumia, Pathologist to the Bryn Mawr Hospital)

Gross Description (See Figure 1) Section of colon measuring 10 cm in length and $2\frac{1}{2}$ cm in diameter with numerous fatty appendages. On the external surface are two cyst-like polypoid growths about 2 cm in diameter, side by side, one appears to be filled with dark red material and the other with dark yellow material. On cut section, there is annular thickening and constriction in the wall of the gut $3\frac{1}{2}$ cm in diameter. Growing from this constriction are numerous polypoid masses.

Microscopic Description (See Figure 2) (1) Generally well preserved mucosa overlying a nodular mass of atypical tissue consisting of broad interlacing bundles of spindle cells, often with fibrillar differentiation, fairly even in morphology with a moderate number of mitotic figures. Certain portions of the tumor contain a very large number of vascular spaces generally without lining. (2) Similar to (1) except that it contains a large nodular mass in which large vessels exist which have a definite wall. (3) Similar to preceding ones, but shows a myxomatous degeneration of the tumor.

Pathologic Diagnosis Hemangiosarcoma of colon, vascular (angiosarcoma)

In view of the unusual nature of this tumor, Doctor Strumia presented the slides to a number of his colleagues at a Pathological Conference at the University of Pennsylvania, Philadelphia, Pennsylvania, and they agreed with his interpretation.

Subsequent Course to Date This patient was next seen on January 25, 1946, for a routine follow-up examination. At this time she had gained weight, was eating well and had no gastro-intestinal complaints. She did mention, however, that she was experiencing metrorrhagia and a gynecologic consultation was advised.

It was not until July 15, 1946, however, that the patient first consulted Dr. Mario A. Castallo for gynecologic examination. At this time, the uterus was found to be the size of a three months' gestation with a large polypoid growth extending from the cervical os to the posterior vaginal vault. On July 23rd, dilatation and curettage and cauterization of the cervix with removal of the polypoid mass, followed by the insertion of 3600 mg. hours of radium in the cervical canal, was done by Doctor Castallo at St. Mary's Hospital, Philadelphia, Pennsylvania.

Microscopic sections of this polyp revealed it to be of a sarcomatous nature closely resembling the primary tumor of the colon. (See Figure 3)

The patient was then sent to Dr. Paul Eberhard at Jefferson Hospital for roentgen-ray therapy. On September 26, 1946, roentgen-ray therapy was started to two anterior and two posterior pelvic ports, and 2000 r were delivered to each port. Another 3000 r was given directly to the original site of the lesion through an intravaginal cone. At the conclusion of this treatment, all evidence of the original lesion had completely disappeared and

FIG 2

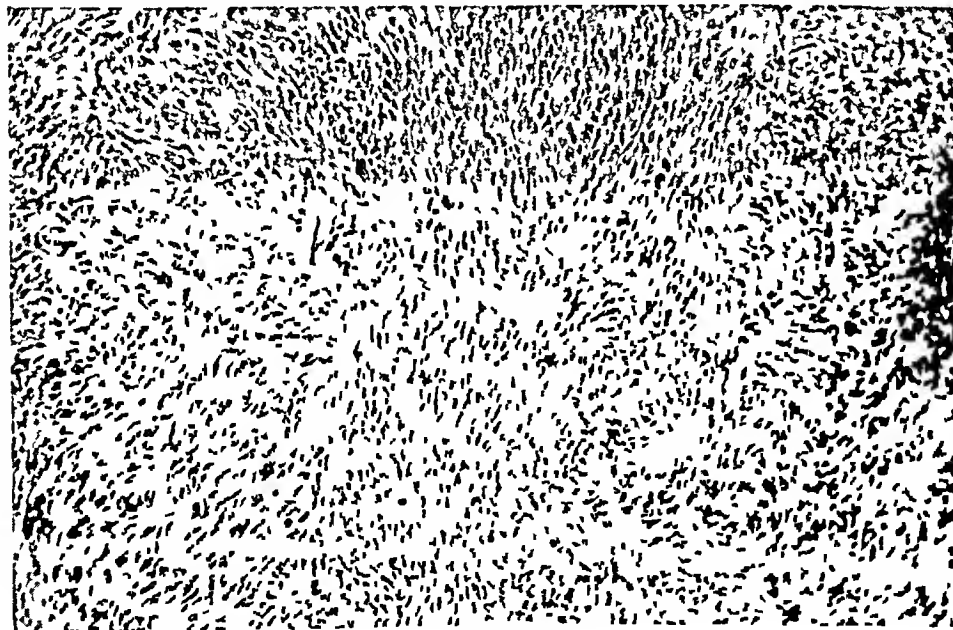
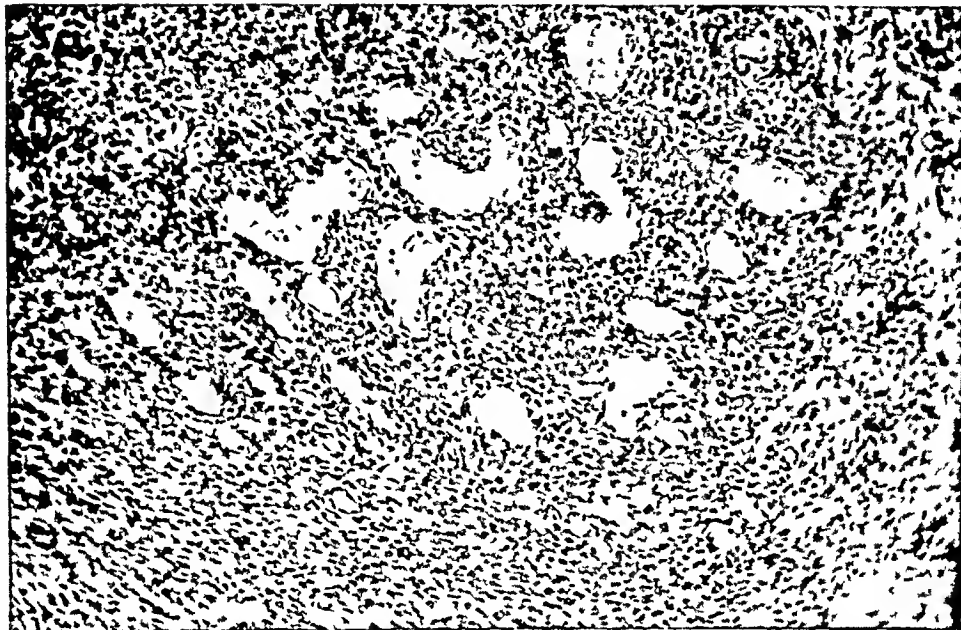


FIG 3

FIG 2—Microscopic section angiosarcoma of sigmoid colon

FIG 3—Microscopic section of sarcomatous uterine polyp

vaginal examination by Doctor Castallo on October 11, 1946, revealed the uterus to be smaller in size with no evidence of recurrence of the polypoid mass

The patient was last seen in September of 1947, at which time examination was entirely negative and the patient was symptom-free

SUMMARY AND CONCLUSIONS

I Less than 400 proven cases of sarcoma of the colon have been described in the literature, and of these, approximately 95 per cent are lymphosarcomas

II A case of angiosarcoma of the colon is presented which we believe is the first to be described

III In the two and a half year interval since resection of the neoplasm, this patient has had no symptoms referable to her gastro-intestinal tract She did develop, however, a uterine polyp which upon removal was found to be of a sarcomatous nature, closely resembling the primary tumor of the colon The relationship between this lesion and that of the sigmoid colon is open to conjecture

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ANNOUNCEMENT

The Buffalo Surgical Society announces the award of the Roswell Park Medal to Dr. Evarts A. Graham for outstanding surgical achievement

Doctor Graham will give the Roswell Park lecture May 5, 1949, at the Kleinhans Music Hall, 9 00 P. M., Buffalo, N. Y.

BOOK REVIEW

DETAILED ATLAS OF THE HEAD AND NECK by R C Truea and C E Kellner New York, 1948, Oxford University Press

This superb work was designed to supply the needs of students and practitioners alike, who are interested in regional anatomy of the head and neck. It contains original presentations of clearly identified structures arranged in "layers" from without inwards, frontal and transverse sections, skeletal structures, and a large section on cerebral anatomy. In contrast to other recently published atlases for use in special fields of head and neck surgery, this volume is all inclusive. Small scale drawings of detailed anatomy of the orbit, jaw, larynx, etc, have been prepared with a view toward clinical application, and the specialist in any field of this part of the body will find them well worth while. Cadavers were specially dissected for the illustrations. Original drawings in each series were made from the same specimen for uniformity of scale. In those instances where the scale was altered, that fact is accurately noted.

The student, especially in his first medical school year, will benefit by using this atlas as a supplement to his major text book. As indicated in the introduction by E A Boyden, the change in emphasis from systemic to regional study of anatomy reflects an "awareness of the inextricable relation between the basic medical sciences and their clinical applications"

HENRY P ROYSTER, M D , Philadelphia

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April 1949

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LETTER TO THE EDITOR

DEAR SIR

The National Paraplegia Foundation wishes to announce the establishment of a limited number of fellowships for research in spinal cord disease and trauma and in the complications commonly associated with such disease or injury. These fellowships carry a minimum stipend of \$3000 per year and may be awarded to any candidate who has demonstrated a capacity for medical research and has outlined a program of meritorious study. The fellowships will be awarded by the Medical Advisory Committee and are open for award for the academic year 1949-1950. Application forms may be obtained from the Chairman of the Medical Advisory Committee, and applications should be submitted to him not later than June 1, 1949.

L W Freeman, M D
Chairman, Medical Advisory Committee
National Paraplegia Foundation
1040-1232 West Michigan Street
Indianapolis 7, Indiana

ANNALS of SURGERY

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TRANSACTIONS OF THE SOUTHERN SURGICAL ASSOCIATION

MEETING HELD AT WHITE SULPHUR SPRINGS, W VA
DECEMBER 7, 8, 9, 1948

ADDRESS OF THE PRESIDENT

THE SURGICAL MAN*†

EDWIN P LEHMAN, M D

CHARLOTTESVILLE, VA

LIKE EVERY PRUDENT PRESIDENT of the Southern Surgical Association, I have looked back to see what my distinguished predecessors have found worthy of presentation on like occasions. Most of them have seen fit to discuss not surgical topics but what might be called parasurgical topics—essays on the position of surgery in society, on its effects upon society, on the men who have made surgery what it is, the color, the texture, even the tall tales of surgery. It is a tradition, both literary and historical, that seems worth preserving. There are not many rostra from which this sort of essay is customarily presented.

The history of surgery in broad or limited aspects has been the predominant subject. The effect of the surgeon's efforts on the development of his art is interesting, but more importantly it is also the kernel of an understanding of modern surgery. Nowhere have I found a discussion of the effect of the practice of surgery on the surgeon. It is this subject that I have taken tonight.

* From the School of Surgery and Gynecology, University of Virginia, Department of Medicine.

† Presidential address, read before the Southern Surgical Association, White Sulphur Springs, W Va., December 8, 1948.

For my title I have shamelessly appropriated in translation a title from an address by Cushing on a somewhat different matter

We are surgeons primarily because of either one or more of several innate qualities which our earliest contacts with medicine have brought to the surface. The choice of a physician's career is based upon a complex pattern of intellectual, emotional and practical considerations that do not concern us here. We are concerned with the considerations beyond these which first set our feet upon the surgical path—in effect, in what particulars we differ as surgeons from other physicians. The first of these—and I believe the most compelling—is delight in handicraft, the primitive fascination of artisanship. No matter how often repeated, the clean division of tissue, the accurate seizure of a bleeding point, the neat placing of a suture, the gentle replacement of the fragments of a fractured bone are skills that give fresh pleasure. The second particular is an intellectual demand for the clear-cut resolution of the obscure. Through a surgical approach, disease is laid bare and the often-murky haze of symptomatology is burnt away. The third is the appeal of a direct attack on disease, positive action for which we assume the responsibility. There is a satisfaction in the prevention of peritonitis by the closure of a perforated ulcer, in the cure of cancer by radical operation, and in many like accomplishments that rest upon our individual decisions and efforts.

A fourth attraction that to unformed minds may be a compelling influence toward a life of surgery is its reputed glamour. To the young man in his first contact with medicine the surgeon may appear in romantic guise. The neophyte has been nurtured on presentments of surgery both in print and in motion pictures which we all know are too often false in emphasis and inaccurate in detail, presentments that describe the life of the surgeon as something beyond ordinary lives in color, in wisdom, in power. His first glimpse of the quiet operating room, the shining walls and the gleaming instruments, the silent masked figures moving efficiently at their tasks under the command of the demigod with the scalpel in his hand does nothing to smudge the colors of the picture he has formed. But let responsibility, even a small share of the responsibility, for the successful prosecution of the surgical ritual fall upon his shoulders and the chromatic tints of the picture vanish, leaving uncompromising lines of workaday black and white. As Aldous Huxley has written "Adventures and romance only take on their adventurous and romantic qualities at second-hand. Live them and they are just a slice of life like the rest." There is no glamour in errors in judgment, clumsiness in manipulation, lack of omniscience, and there is no calling in which such defects are more cruelly paid for. Let me not put this matter too naively. There are a few of us, Thespians all, to whom glamour is still a living force in the daily course of surgery. The rest of us, the great majority, can perhaps envy the preservation of an illusion which must do much to compensate for the dark periods of self-condemnation and remorse.

However, the reporters and the novelists and the scenarists have somehow largely missed what to me at least remains a daily drama. It has been missed

because it is not a drama of action and responsibility, but rather a quiet drama of the mind, living only in the awareness of one who has experienced it. Just ahead lies action, the necessity to pit knowledge and judgment and technical skill against the unknown. Yet before the attack can be opened, a period of contemplation is enforced. For a timed course of minutes that sometimes seems interminable the surgeon must stand quietly and perform the rhythmic movements of the scrub. His hands may be supplied, but the tensions in his mind are apt to grow and the need for self-control to become more and more imperative. According to Bliss Periy, Harvey Cushing spoke of the "cerebral excitement" of this period. With the exception of the concert pianist or violinist who may increase the blood flow to his hands and arms by soaking them in warm water before emerging from the wings, there are few occupations in which repose always must precede decisive action.

The qualities of the surgical life that tend to attract physicians to surgery are then fundamentally three—delight in handicraft, the satisfaction in an unequivocal answer to a diagnostic mystery and the appeal of a purposeful and decisive attack. You will note that the aspects of life common to all doctors are not included, such as the daily contact with physical and mental distress, the dedication to its relief and the things that the last implies—observation, reading, investigation. You will note also that nothing is said of material rewards.

What qualities in man does this sort of life breed? In attempting to find the answer to this question, one must not assume that no other occupation, medical or nonmedical, will breed like qualities. As a matter of course, these qualities are the result of living successfully any sort of adjusted life. Perhaps this particular sort of life has a tendency to foster certain of the finer possibilities with which, in spite of a massive disillusionment created by the modern international scene, I still believe all men are primarily endowed. And here another assumption must be categorically denied. Let no one say that the tendency of the surgical life to foster certain qualities means more than it says. One must not imply that the result is necessarily a perfect race of men, the demigod of the novel and the screen. Let us be thankful only that the life we live tends to cultivate our larger qualities rather than the littleness that lies in us all. The mechanism is simple. If we would be good surgeons—an aim common to every one of us—these qualities must grow in us.

The first of them is intellectual honesty. If we have not that we do not rate the honored name of surgeon. An honest appraisal of errors and ignorance and an honest acknowledgment of them to oneself, to colleagues and to juniors comprise normal behavior. The surgeon may often dread the autopsy table, but he does not try to conceal error by discouraging postmortem examination. It is, perhaps, significant that when all sorts of ill chances were being imaginatively referred to a fantastic race of gremlins, no surgeon predicated a gremlin that breaks the ligature at a critical moment, or pushes the bowel upon the blade of the knife as the peritoneum is opened, or hides the stone in the recesses of the common bile duct, or seeds the hernia wound with streptococci.

These disasters are commonly the cause for self-examination, critical and searching, and any other reaction, even that of placing deserved blame on some other member of the operating team, must await a rigid exoneration of oneself.

A second quality bred by the practice of surgery is intellectual curiosity. It is not without meaning that many of the fundamental contributions to our knowledge of the mechanisms of the human body have been made by men who were primarily surgeons. The membership of our own association contains those whose studies of physiology both normal and abnormal have been illuminating to the whole field of medicine. It is natural that this should be so. No one could be more deeply concerned with physiologic mysteries than the surgeon who has seen his pathologic knowledge and technical skill go for naught when the patient succumbs in a manner not explained. The fact that so often surgical exploration explains the hitherto mysterious makes all the more harassing a failure to understand clearly. Surgery offers day in and day out a stimulus to the widening of man's knowledge of man's disordered body.

A third effect of surgery on the surgeon is the development of what might be called a rational approach to suffering. It is probable that a surgeon in a busy life has caused by his deliberate action more physical pain with its attendant emotional distress than any other single individual except an Inquisitor of the Middle Ages or the commandant of the Gestapo, the M V D or the concentration camp. Yet no one considers the surgeon a cruel man. His behavior is genuinely kind. He measures the evil of postoperative suffering against the evil of suffering from disease. When one contemplates this daily balancing of evils one against another, it becomes evident that sentimentality can have no part. The surgeon is fortunate to be relieved, by the very nature of the decisions he must make, of the burden of a superficial emotion that can confuse rational behavior.

In the fourth place, surgery breeds equanimity in difficult times. To quote from Osler's classic essay* "Now a certain measure of insensibility is not only an advantage but a positive necessity in the exercise of calm judgment and in carrying out delicate operations. Keen sensibility is doubtless a virtue of high order, when it does not interfere with steadiness of hand or coolness of nerve." Surgeons are faced with situations that try equanimity to its veriest limit. The escape of a cystic artery from control in the remote depth of an obese abdomen, a rapidly enlarging wound in a paper-thin obstructed bowel, the contamination of an essential instrument at a critical moment, the error of a trusted assistant, a sudden failure of the patient's respiration or heart beat, each of these, various as they are, calls for a degree of self-control that must permit immediate action accurately adjusted to the particular emergency. We must pity the rare surgeon who explodes under such circumstances. It is only by cool decisiveness that these not uncommon disasters can be effectively met.

Equanimity is closely related to courage, the fifth quality surgery fosters in the surgeon and the last that I mention. Courage is often necessary to maintain equanimity or to exercise complete intellectual honesty, but as a separate entity

* "Aequanimitas"

it has characteristics of its own. It is the quality that enables the surgeon to assume responsibility for the remote chance of helping the desperately ill patient no matter what the risk. It is the quality that refuses to consider mortality rates or public reaction. It is fearlessness of any consequence except harm to the patient. It is the determinant of action in the cool moments before action begins, before the heat and the pressure of the emergency. It is bold decision while yet there is time to think, decision made in the lonely black depths of one's consciousness without emotional support of cheering crowds or martial music. Surely there is no calling that so often demands the sort of calm reasoned courage that is the best that man can offer to the world.

Now all this smacks of a nobility that no breed of mankind can possibly boast. Note well again that I have said that the practice of surgery only fosters these fine traits of character, not that it inevitably develops them. We are imperfect humanity, subject to all the weaknesses of intellect and emotion, the defects of character that have led man to his present not too happy state. Since we are subject to these imperfections, let us not forget that the life of a surgeon may foster some of the less amiable qualities of man. Let our wives, our assistants, the nurses in our operating rooms and wards testify to the occasional pettiness of our demands and the bursts of temper that may greet failures to meet them. I doubt not they would be eloquent. The conditions of surgical action which always must seek perfection in detail make such behavior easy. At the risk of moralizing let me say that this fact serves as an explanation only, hardly as an excuse.

There is one result of the common life we lead that is uniformly good. We like each other. We know the trials that we all face, and no one but a surgeon can know them in all their fullness. We know that each of our colleagues has cultivated a modicum of the nobility inherent in the surgical art, enough, at least, to place him where he stands today. We are drawn together into a guild by our common problems and then common solutions. We wonder if any other craft can unite in such mutuality of emotion as we instinctively display. It is proper that we so wonder. If we did not, the essence of our unity in surgery would be imperfect. "We be of one blood, ye and I."

Friendships may be classified upon three levels: abdominal, thoracic and cerebral. Abdominal friends enjoy the good things of life together such as we have enjoyed tonight. Thoracic friends are attuned in emotional responses—kindness, honesty, equanimity, courage. Cerebral friends experience curiosity regarding the same mysteries, face common intellectual problems from the same direction and seek with the same tools of reason the answer to the unknown. In the three categories of friendship, surgery knits us together. I, for one, would belong to no other fellowship.

SEX RATIO EXPERIMENTAL STUDIES DEMONSTRATING CONTROLLED VARIATIONS—PRELIMINARY REPORT*†

DERYL HART, M D , AND JAMES D MOODY, M D

FROM THE DEPARTMENT OF SURGERY DUKE UNIVERSITY SCHOOL OF MEDICINE
AND DUKE HOSPITAL

EXPERIMENTAL WORK, carried out in an effort to determine the factors responsible for intra-uterine sex differentiation, has been almost without limit, while the positive results have been meager. Theories as to the factors responsible for this sex differentiation have been as varied as the experimental work. Our interest in this age-old problem was aroused by the clinical observation that when insemination occurred early in the fertility period the resultant offspring was more likely to be a female, and when insemination occurred late in the fertility period the resultant offspring was more likely to be a male. The concept was drawn from these observations that the sex of the fetus may be determined directly or indirectly by the time relationship between insemination and ovulation. The experimental work and a statistical analysis of the sex distribution in human twins, herein reported, were performed in an attempt to confirm or disprove this.

In order to make clearer the bearing on the present study of certain data gathered from previously published work, it seems desirable at this time to present our concept in diagrammatic form (Fig 1).

In the middle of the fertility period the sex ratio is presumed to be approximately equal. As one increases the time interval between insemination and ovulation, either before or after ovulation, there is an increasing predominance of one sex. In making the diagram (Fig 1), we have used the figures from our experiments on late insemination, and these show the male predominance in the latter part of the fertility period. It has been presumed, with some supporting data, that a female preponderance is probable in the early stages of the fertility period. It should be understood that the sex pattern as illustrated is based on our experiments with rats and our analysis of human twins and may not apply to every species.

HISTORICAL

It is nearly impossible and also unnecessary at this time to summarize even briefly, all the experimental and clinical work performed on the problem of predetermination of sex. In this vast amount of material, we found certain data that tended to uphold the above-mentioned concept. For example, in 1934, Hammond¹ made a study of fertilization of rabbit ova in relation to time intervals following mating. Knowing that rabbits will ovulate approximately 10 hours following mating, he first mated female rabbits with vasectomized males to stimulate ovulation and then with normal males for insemination at different time intervals. The results are given in Figure 2. There

* This study was aided by a grant from the U S Public Health Service

† Read before the Southern Surgical Association, White Sulphur Springs, W Va, December 7, 1948

SEX RATIO

is a marked shift in the sex ratio, giving a preponderance of males as the time of insemination approaches the time of ovulation. Although we are unable to explain the sudden reversal in sex ratio at the time of ovulation and two hours later, the sharply increasing curve in favor of the male sex as insemination

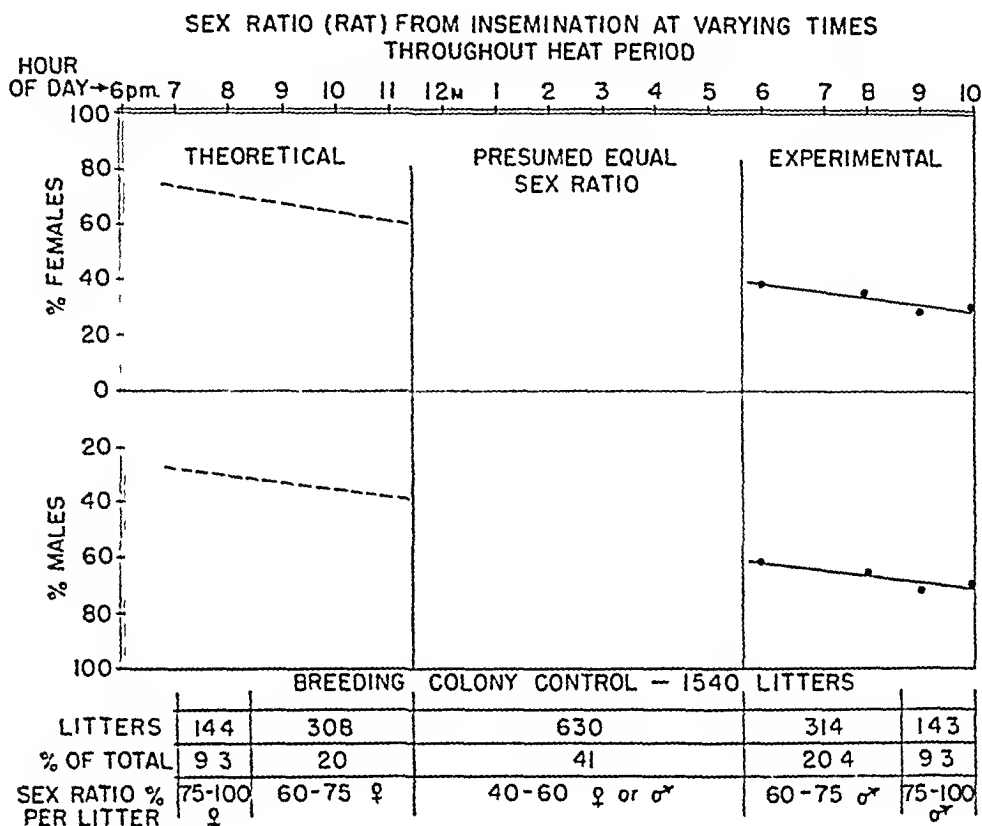


FIG 1—This chart on sex ratio represents in general our idea of the effect of the time relationship between insemination and ovulation on the sex of the offspring. The right part of the graph is plotted from the actual sex ratio in the litters of rats resulting from delayed inseminations. It is obvious that in this portion of the heat period insemination results in a high preponderance of males. It can be readily assumed that, in the middle of the heat period there is a broad band, during which time the majority of inseminations occur, and the sex ratio is approximately equal. In view of the fact that in our breeding colony the offspring are approximately equally divided between males and females, the preponderance of males on the right must be counterbalanced with a like preponderance of females. This preponderance of females we have assumed to result from inseminations occurring early in the heat period. This is theoretical and is shown by the dotted lines on the left of the graph. We have analyzed each litter in the breeding colony and have grouped these according to the varying sex ratios as indicated. The space given for each group is based on the actual percentage relationship the litters in the group bear to the total number of litters. The similarity of this distribution to the experimental and theoretical sex ratio plotted above is very striking.

ination approaches ovulation certainly seems significant. When the figures are broken down to compare various litter sizes (Fig 3), the variation in sex ratio is still striking in the larger-sized litters.

These figures, then, would tend to make one believe that varying the actual time of insemination in the rabbit from the normal time of 10 hours prior to ovulation to a shorter period of time directly influences the resulting

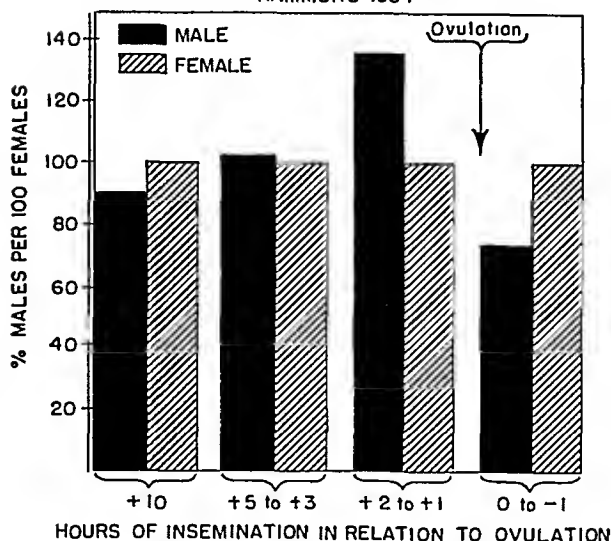
FERTILIZATION OF THE RABBIT OVA IN RELATION TO TIME
HAMMOND 1934

FIG 2—In these experiments normal females were mated with vasectomized males to stimulate ovulation, which is known to occur approximately 10 hours later. At the times indicated, these same females were inseminated by mating with normal males. The resulting offspring show an increasing percentage of males as the time of insemination approaches the time of ovulation. We offer no explanation for the reversal of this trend within the period of two hours following ovulation.

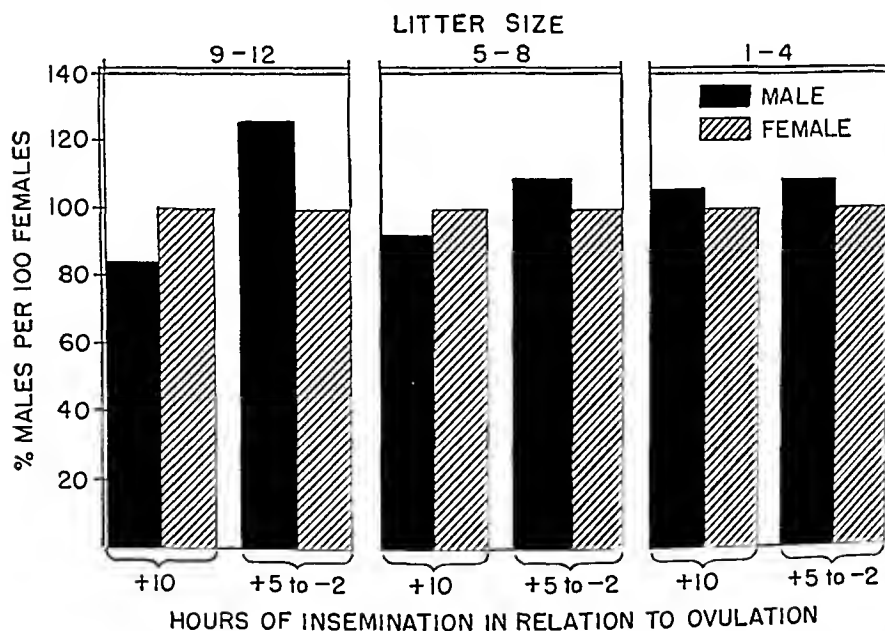
FERTILIZATION OF THE RABBIT OVA IN RELATION TO TIME AND LITTER SIZE
HAMMOND 1934

FIG 3—This figure shows a further analysis of the results given in Figure 2, obtained by breaking them down into the varying litter sizes as shown. There is still an increase in the percentage of males following the inseminations near the ovulation period even though the results for the inseminations for the two-hour period following ovulation are included. The greater increase occurs in the larger litter sizes.

sex ratio in favor of the male. It is entirely supposition, but, at the same time, one might advance the theory that insemination prior to the 10-hour period might result in a sex ratio with a predominance of females.

In this animal, since ovulation is not cyclic but is stimulated by and follows mating by approximately 10 hours, it must be presumed that mating occurs

DELAYED INSEMINATION IN THE RAT
BLANDAU AND JORDAN 1941

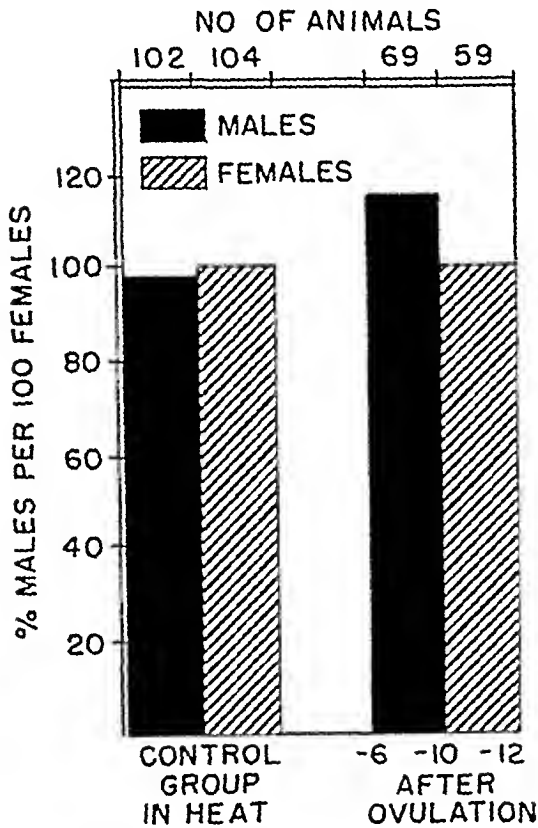


FIG 4

ARTIFICIAL INSEMINATION IN THE HUMAN - SEX RATIO
(SEYMOUR AND KOERNER 1941)

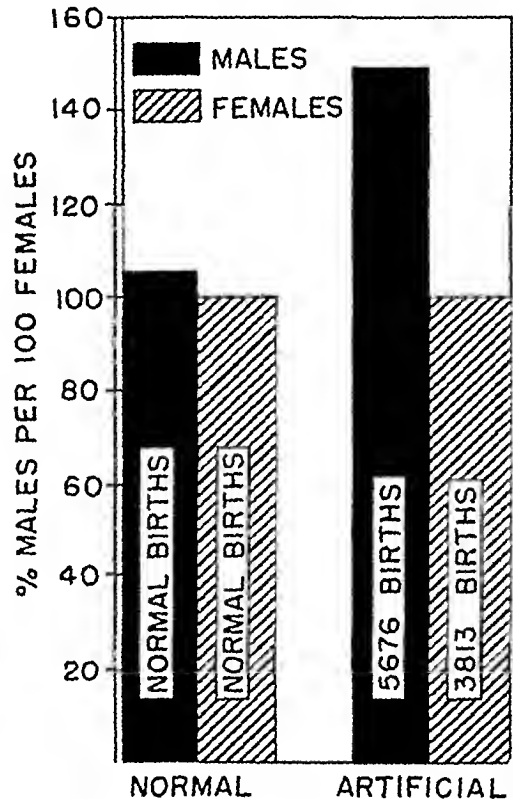


FIG 5

FIG 4—These are incidental figures from a study of the development of the rat ovum following late fertilization by artificial insemination. The increase in the percentage of males is in agreement with the concept expressed above and illustrated in Figure 1.

FIG 5—This great male preponderance as compared to the general birth ratio of approximately 105 males per 100 females is statistically highly significant and must be based on some factor connected with the artificial insemination. The inseminations were relatively infrequent. In the cases in which an attempt was made to determine the time of ovulation, the insemination probably followed this event. Consequently, the number of inseminations occurring following ovulation was probably higher than would be the case under conditions of normal sexual activity, and it is our opinion that the increase in the percentage of males is a direct result of this.

at the optimum time for fertilization and for the production of the sex ratio best suited for the propagation of the species. Consequently, the figures given fit in with our concept, since the onset of mating probably represents the point of the fertility period optimum for the even distribution of sexes. Variations in the time of insemination from this optimum point toward the end of the fertility period are shown to give a preponderance of males.

A second report giving experimental results on delayed insemination in

the rat further substantiates this concept. In a study of the effect of delayed fertilization on the development of the rat ovum, Blandau and Jordan in 1941² reported their results on a large group of animals inseminated at various hours following ovulation. The results are given in Figure 4. There is an increased percentage of males in the offspring resulting from inseminations from 6 to 12 hours after ovulation. Unfortunately, the results for each of the three time periods (Fig 4) are not available. If these were broken down into the three groups, the results might be more striking.

The following reports give data which we consider to have a definite bearing on this concept in its relation to the human sex ratio. Seymour and Koerner in 1941,³ by circularizing physicians, collected 9,489 births resulting from artificial insemination. In this group there was a preponderance of males

TABLE I—*Twins Reported by Greulich*

Distribution into Monozygotic and Dizygotic Groups			
A		B	
As Reported		Distribution Based on 25.5 of Twins Being Monozygotic	
Unlike sexed dizygotic	171	Monozygotic	137
Like sexed		Dizygotic, unlike sex	171
Dizygotic	128	Dizygotic, like sex	230
Monozygotic	96	% like sex as compared with unlike sex in the dizygotic group	134.5
Undetermined	143		

(5,676 males to 3,813 females). The normal sex ratio of 105 males to 100 females would have resulted in 4,861 males to 4,628 females. The collected series therefore showed a 48 per cent increase in the males over the theoretically expected number (Fig 5). This increase might be attributed to the fact that, in so far as the time of ovulation could be determined, artificial insemination was probably carried out at or following ovulation in a larger percentage of cases than would occur in the normal course of sexual relationship. If such were the case, the high preponderance of males could be readily explained on the concept expressed in Figure 1.

Greulich in 1934⁴ reported 538 sets of twins as classified in Table I, Section A. There is a total of 171 unlike-sexed to 271 like-sexed twins after the definitely monozygotic group (96) has been eliminated. Greulich, on a study of body characteristics, and Guttmacher,⁵ on the basis of placental studies, arrived independently at a figure of approximately 25.5 per cent as representing the percentage of all twins that are monozygotic. If all the twins reported by Greulich are considered on this percentage basis, we get the distribution given under B, Table I.

For the dizygotic group this leaves us with a definite preponderance of the like-sexed twins (230) as compared with the unlike-sexed (171). On the basis of chance alone, the number of unlike-sexed twins in the dizygotic group would be balanced by the same number of like-sexed twins. After balancing unlike-sexed with an equal number of like-sexed we are left with a surplus of 59 like-sexed dizygotic twins. This preponderance can be explained readily

by our concept as resulting from inseminations occurring either early or late in the fertility period

The percentage distribution of monozygotic and dizygotic twins as given in the articles of Greulich and Guttmacher enable us to utilize the figures on twins given in the vital statistics of the United States. In the publications available (1941, 1942, 1945^{6, 7, 8}) these were broken down into unlike- and like-sexed male and female. There were a total of 86,996 sets of twins and 827 sets of triplets accurately differentiated as to sex. These are recorded by years for twins as given in Table II, while the small number of triplets are

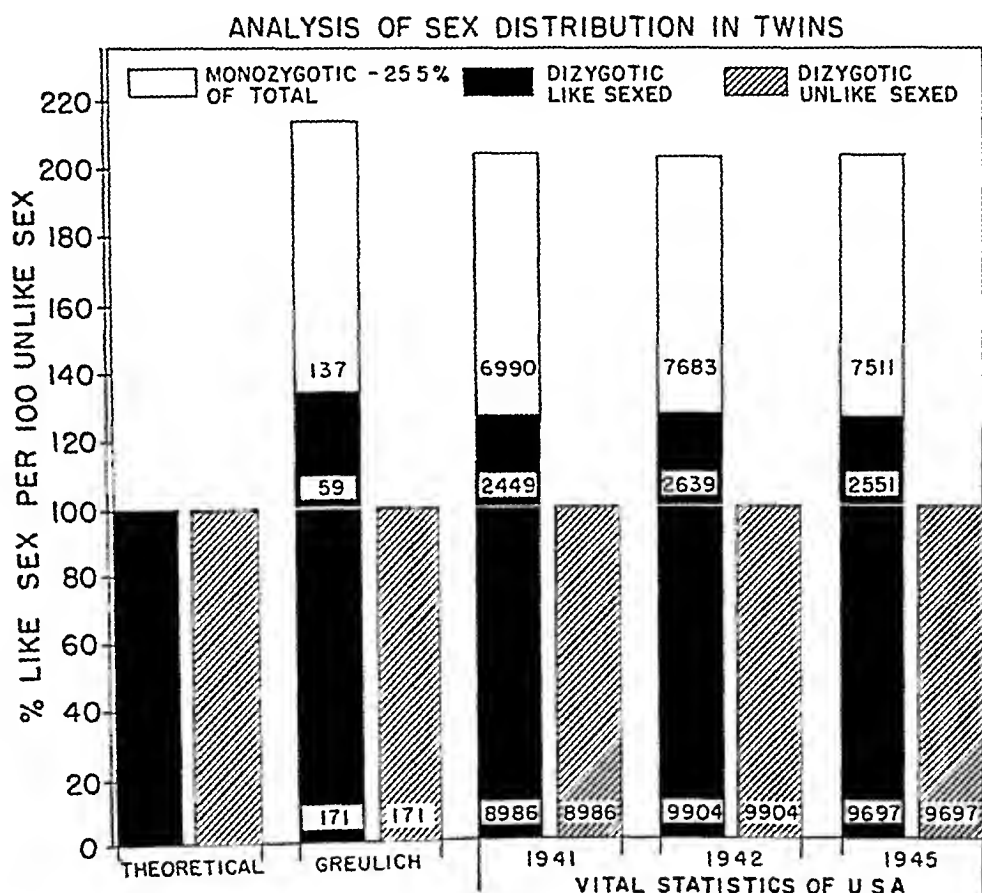


FIG 6—Among twins, both in Greulich's series and in the U S Vital Statistics reports, there are more than twice as many like-sexed as unlike-sexed. A considerable part of this excess is accounted for by the single-ovum twins, which must be like-sexed. In the dizygotic group, by chance alone, there should be an even distribution of like- and unlike-sexed twins. However, as shown, there is a surplus in the like-sexed dizygotic twins ranging from 26 to 34 per cent. As explained in the text and in Figure 7, we believe this surplus is accounted for by inseminations occurring both early and late in the fertility period.

combined as given in Table III. For the twins, the table shows a breakdown into monozygotic male and female groups and dizygotic unlike- and like-sexed groups, with the latter further divided into groups of males and females. From this table and from Greulich's figures we have plotted Figure 6, showing the preponderance of the like-sexed over the unlike-sexed in the dizygotic groups. For Greulich's group this ratio was 134.5 per 100, while for the much larger

TABLE II — *Vital Statistics of the United States—Twins*

Year	Cases of				Like Sex										Unlike Sex	
	Twins		Total		Total		Both ♀		Both ♂		Total ^b		Monozygotic		Total ^c	
	Total Births	Unlike Sex	Total	Sex	Total	Sex	No	% of Total	No	% of Total	No	% of Total	♀ ^e	♂ ^d	Total ^e	♂ ^f
1941	2 513 427	8 986	27 410 ^a		18 424		9 041	49 08	9 383	50 92	6 990	3 431	3 559	11 434	5 612	5 824
1942	2 808 996	9 904	30 130 ^a		20 226		9 868	48 08	10 358	51 2	7 683	3 749	3 934	12 543	6 119	6 424
1945	2 735 456	9 697	29 456		19 759		9 699	49 09	10 060	50 91	7 511	3 687	3 824	12 248	6 012	6 236
Column Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18

^a Does not include 29 cases (1941) and 26 cases (1942) with sex unknown^b through ^c references to column figures are for same year^d 25 5%^x of total cases of twins column 3^e The percentage column 7 of total monozygotics column 10^f The percentage column 9 of total monozygotics column 10^g 74 5%^y of total cases; twins column 3 less cases unlike sex dryzygotes column 16^h Total cases like sex females column 6 less cases monozygotic females column 11^z Total cases like sex males column 8 less cases monozygotic males column 12^b Same as column 4—unlike sex must be dizygotic^x Percentage of twins—
Monozygotic } Almost identical figures were arrived at independently by Greulich in a study based on body characteristics and by Guttmacher in a study based on placental arrangement^y Percentage of twins—
Dizygotic }

DISTRIBUTION OF LIKE AND UNLIKE SEXED DIZYGOTIC TWINS (US Vital Statistic Reports) IN CORRELATION WITH THE SEX RATIO GRAPH GIVEN IN FIG 1

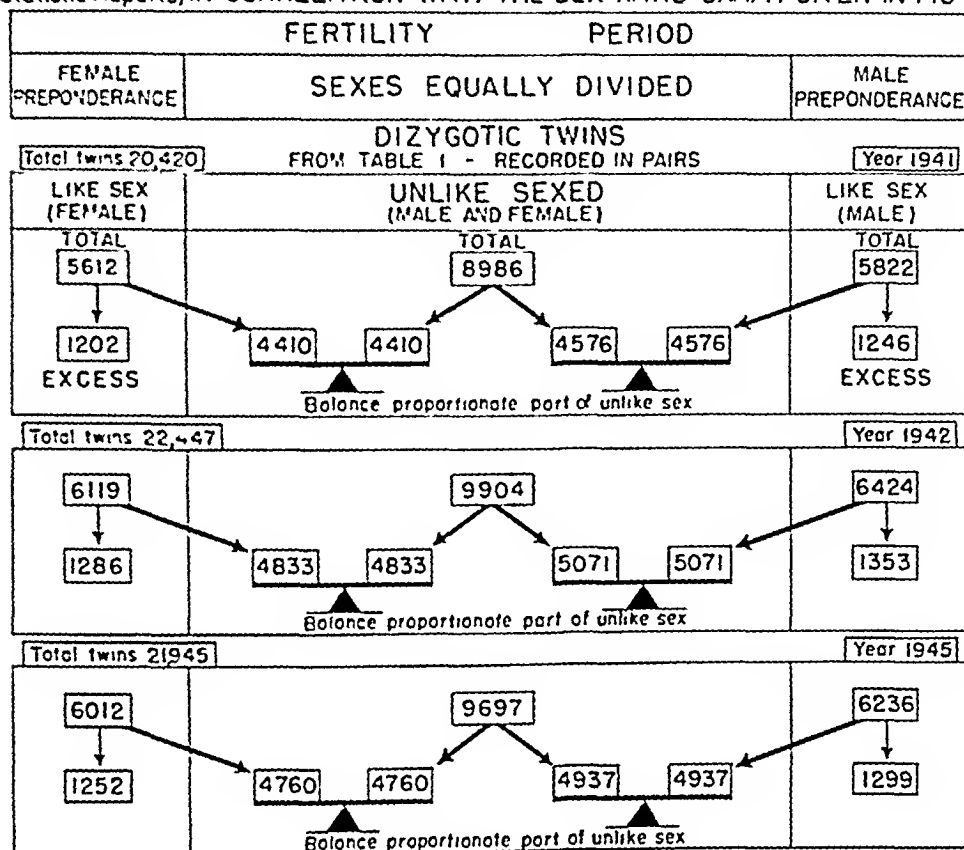


FIG. 7—Dizygotic or double-ovum, twins give us an excellent approach to this problem through statistics already available. If the concept as explained above is correct namely, that early insemination results in a preponderance of females and late insemination results in a preponderance of males, there would necessarily be a preponderance of like-sexed dizygotic twins. Those resulting from early inseminations would be predominantly like-sexed females, those from late inseminations predominantly like-sexed males while those resulting from inseminations in the mid-fertility period would by the law of chance, be equally divided between like and unlike sexes.

The upper part of this graph shows the times of insemination which, in our opinion, result in female preponderance, relatively equal sex distribution and male preponderance. This is patterned after Figure 1.

The lower part shows in the mid-fertility period, the unlike-sexed dizygotic twins balanced with an equal number of like-sexed dizygotic twins, the latter divided between females and males in the ratio of the total like-sexed females to the total like-sexed males for the year. There is a surplus of both like-sexed females and males which cannot occur consistently in such large numbers and in such a constant ratio by chance alone. Therefore, we feel that chance alone as an explanation of the relatively equal ratio of the sexes, even in single births, is untenable. Such a distribution of like- and unlike-sexed dizygotic twins can be explained only by the premise that in a certain portion of the fertility period insemination is more likely to result in female offspring, while in another portion insemination is more likely to result in male offspring, and these figures therefore can best be explained by the concept advanced by the authors.

census figures the ratio was 127.3, 126.6 and 126.3 per 100 for the years given. This preponderance of the like-sexed over the unlike-sexed in the dizygotic group is beyond the possibility of chance.

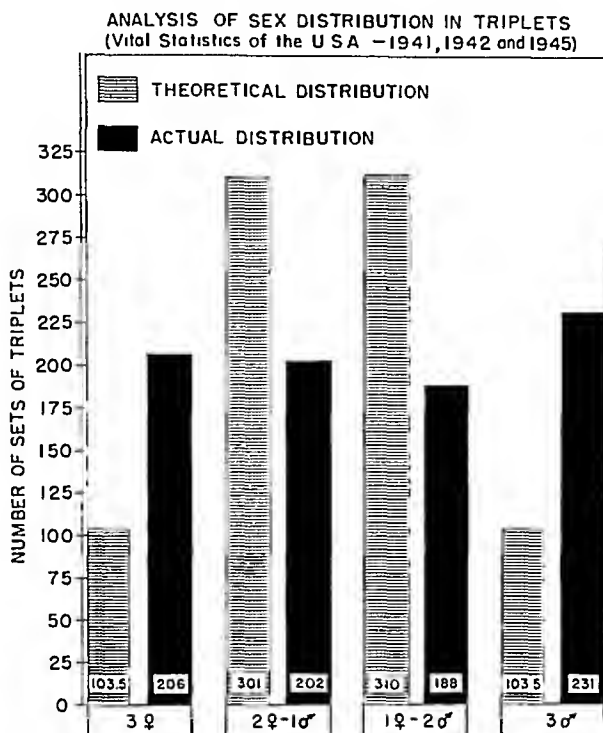


FIG. 8—The figures given above are taken from Table III and show the marked deviation of the actual sex ratios from a theoretical distribution based on chance. There is a great increase in the number of like-sexed males and females over the expected number based on chance, and this seems to be greater than would be expected on the basis of monozygotic triplets alone.

TABLE III—Vital Statistics of the United States—Triplets

Year	3 Females	2 Females 1 Male	2 Males 1 Female	3 Males	Total
1941	70	63	62	74	269
1942	69	75	61	85	290
1945	67	64	65	72	268
Total	206	202	188	231	827
Theoretical distribution by chance	103.5	310	310	103.5	

We have no statistical data on which to base a differentiation into monozygotic and dizygotic groups. A comparison with Table I shows that the percentage of three of like sex as compared to the 2:1 distribution is almost as high as the two of like sex is to the 1:1 distribution among twins, even though statistically it should be much less.

In Figure 7 the statistics from Table II have been further broken down to show the distribution of the excess number of like-sexed dizygotic twins into male and female groups. As set forth in the legend, we have shown that there

is only one explanation for this, namely, that there has to be some portion of the fertility period during which insemination results in a preponderance of females and another portion when insemination results in a preponderance of males. The distribution of this excess number of like-sexed dizygotic twins in Figure 7 is arranged so as to explain them on the basis of early and late inseminations as advanced in the authors' concept.

The United States Vital Statistics for the years 1941, 1942 and 1945 report 827 sets of triplets with the sex distribution recorded (See Table III) and two sets of triplets with the sex unknown.

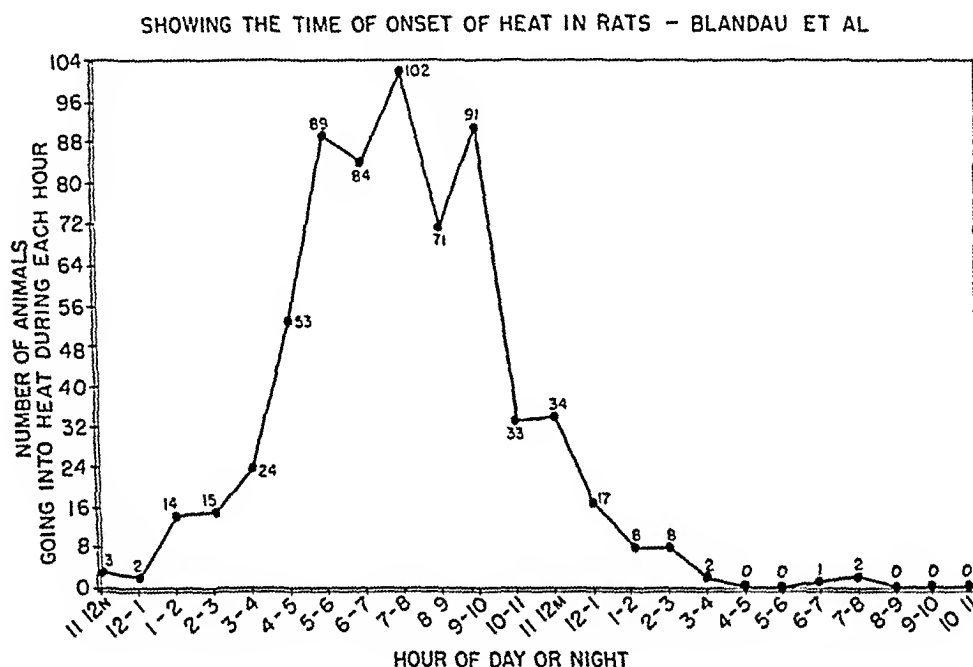


FIG 9—This graph, plotted from the published work of Blandau and his co-workers, shows the time of onset of heat in rats as determined by the copulatory response. The experiments here reported are based on the fact that the great majority of rats go into heat within a relatively short space of time centered at about 7 P.M. It was realized that all rats going into heat after 10 P.M. would diminish the expected male preponderance from inseminations carried out from 6 to 10 A.M., but it was felt that statistically significant results could be obtained in spite of this.

From the figures given in Table III we have plotted the graph in Figure 8. This shows the preponderance of like-sexed females and males to be more than twice as great as would be expected from chance alone. Since we have no statistics indicating the percentage of monozygotic triplets, we have been unable to plot this graph on the basis of triplets resulting from fertilization of separate ova. However, the marked divergence of the sex ratio from the theoretical distribution of sexes based on chance is sufficiently great to appear significant, even though the monozygotics have not been eliminated (Compare with Fig 6).

MATERIAL AND METHODS

Experiments were first undertaken with rats since much was already known about their sexual behavior, since they are relatively inexpensive to maintain, and are highly productive, with a relatively short gestation period. Animals

for the experiment were taken from our own breeding colony of the Osborne-Mendell strain since we had accurate statistical data on the sex ratios covering the years since 1937, which could be used as a control

At the beginning of the experiment in 1946 and 1947 the living quarters for this colony were not comparable with those of the control group. The cages were crowded, lighting was inadequate and adequate temperature control was impossible. The diet of the control and the experimental groups has always been identical. At the beginning of 1948, adequate cage space was obtained in a well-lighted, properly ventilated room with time-controlled light switches.

VARIATIONS IN THE SEX RATIO IN RATS DEPENDENT ON THE TIME RELATIONSHIP BETWEEN OVULATION AND INSEMINATION (WITHOUT CONTROLLED LIGHTING-1947)

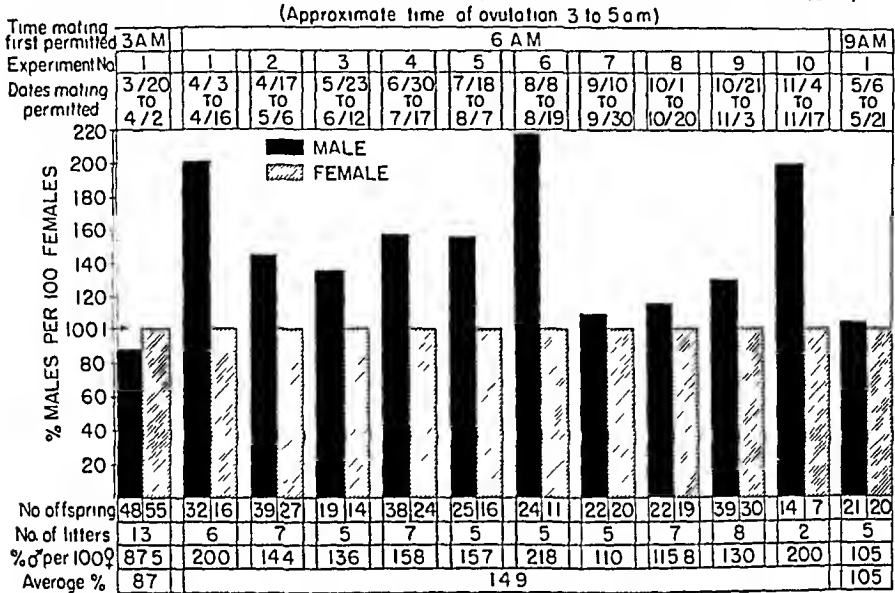


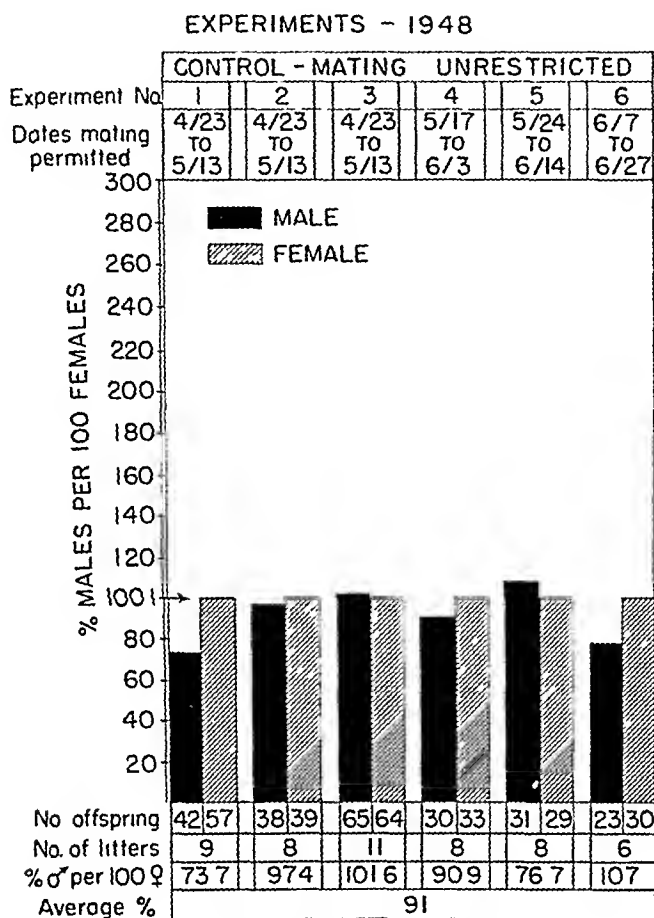
FIG 10—This graph shows the first experimental results obtained. As noted in the text, in the first experiments at 3, 6, and 9 A.M. only the 6 A.M. group showed a marked male preponderance. Since, with the limited facilities, only a few experiments could be run, it seemed desirable to concentrate on the 6 A.M. group to determine whether or not a male preponderance would be constant. This proved to be the case, as shown in the graph, despite the fact that defective equipment, discovered only toward the end of the experiment, may have at times permitted mating earlier than the scheduled hour given on the chart. Such uncontrolled matings may have accounted for the results of these experiments being less significant statistically (49 per cent increase in males) than those obtained in the better-controlled experiments in 1948 (68 per cent increase in males for the 6 A.M. group) Figure 11B. The 100 per cent mark indicates the ratio of males per 100 females in the breeding colony and the 49 per cent increase in males was based on these figures as a control.

From this time on the laboratory was kept dark from 8 P.M. until 6 A.M. throughout the year, giving a constant daily 14-hour light period. Temperature regulation has been improved, being thermostatically controlled at 84° F during the heating season, but the laboratory has not been air-conditioned for the summer.

It was felt that the easiest approach to this problem was to produce pregnancies by inseminations through normal mating, permitted only at definite

SEX RATIO

times in the latter part of the heat period (Figs 10 and 11) This we have assumed to be the latter part of the fertility period This was done by placing sexually mature male and female rats in adjoining cages connected by a short, closed runway The latter was opened automatically by a time-controlled mechanism set each evening The trap door was a solid sheet of metal which shielded one cage from the other



A

FIG 11A—The major control for all these experiments was the output for one year of the medical school breeding colony from which these experimental animals were taken With more than 12,000 offspring there was a sex ratio of 100:1 males per 100 females In addition, we ran a further control, using six of the same groups of animals as used in the experiments These gave the sex ratio as shown above (Part A) with an average of 91 males per 100 females The 6, 8 and 9 A M experiments (where there was no chance of earlier mating—see Fig 10) show a progressive rise in the percentage of males from 168 to 255

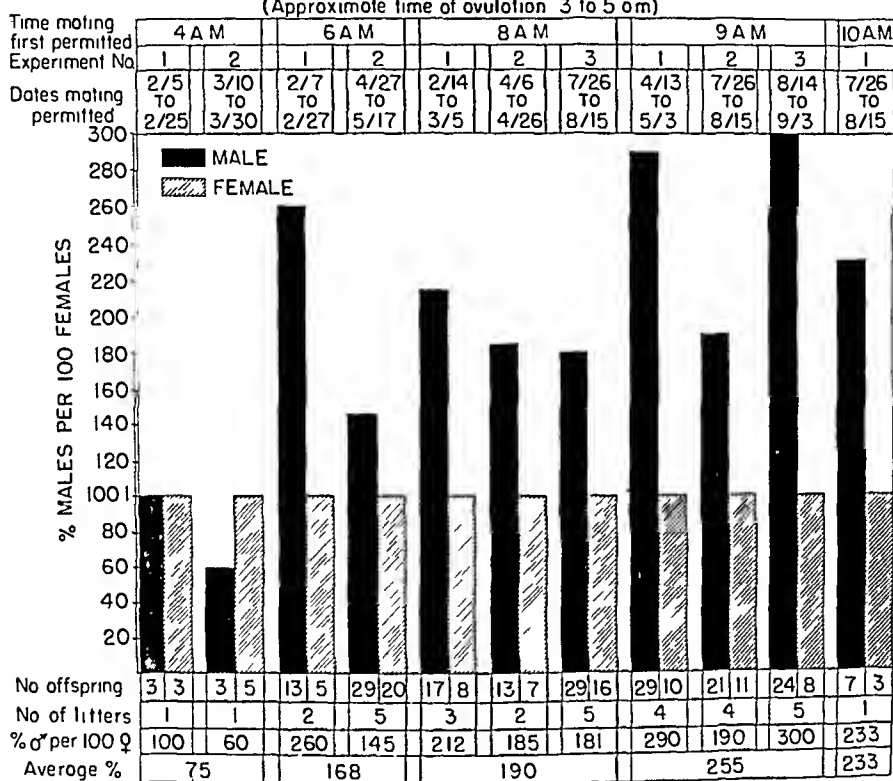
Mating was permitted daily over the period of time and beginning at the hour indicated on the charts (Figs 10 and 11) Groups of 15 females were used with corresponding groups of six males The females were left in their cage continuously over this period while the males were used in rotation daily

in groups of two. The sexes were separated daily between 9 and 11 A.M. Handling was kept to a minimum.

After the total period of mating, the group of females was isolated for 24 days. Rats which became pregnant were removed from the group before the termination of gestation and returned to the group after weaning the litter at 21 days. Each group was discarded after four experiments.

When a litter was born, the sex of each offspring was determined by the anogenital distance.⁹ The young were allowed to grow to 21 days, at which time they were weaned and the sex of all survivors was checked again as a

VARIATIONS IN THE SEX RATIO IN RATS DEPENDENT ON THE TIME RELATIONSHIP BETWEEN OVULATION AND INSEMINATION (WITH CONTROLLED LIGHTING - 1948)
(Approximate time of ovulation 3 to 5 a.m.)



B

FIG 11B—There was only one litter in the 10 o'clock group and this showed a male preponderance of 233 per cent. From these figures, one would conclude that there was evidently some error in the 9 A.M. group in 1947 (Fig 10), probably the result of early mating due to defective equipment. Analysis of these figures in the delayed-insemination groups show them to be highly significant and almost certainly beyond the possibility of chance.

control against the primary sex differentiation. Whenever possible, the sex of any rat dying within the 21-day period was also checked.

RESULTS

These experiments can be divided into two groups. The first of them, done in 1947, were performed under somewhat unsatisfactory conditions and the second in 1948 under much improved conditions, as noted above. The total

output of the medical school breeding colony for the year beginning November 3, 1945, is taken as a control for both the 1947 and 1948 experiments. In this year, with 12,135 offspring reaching the age of 21 days, at which time they were sexed, there were 6,071 males and 6,064 females in a total of 1,540 litters or a ratio of 100.1 males per 100 females. The sex ratio by litters is given in the chart of Figure 12. During the past two years, all large litters have been reduced to eight at the time of birth, without any attempt to determine the sex of the discards. For these years, 11,202 (5,670 males and 5,532

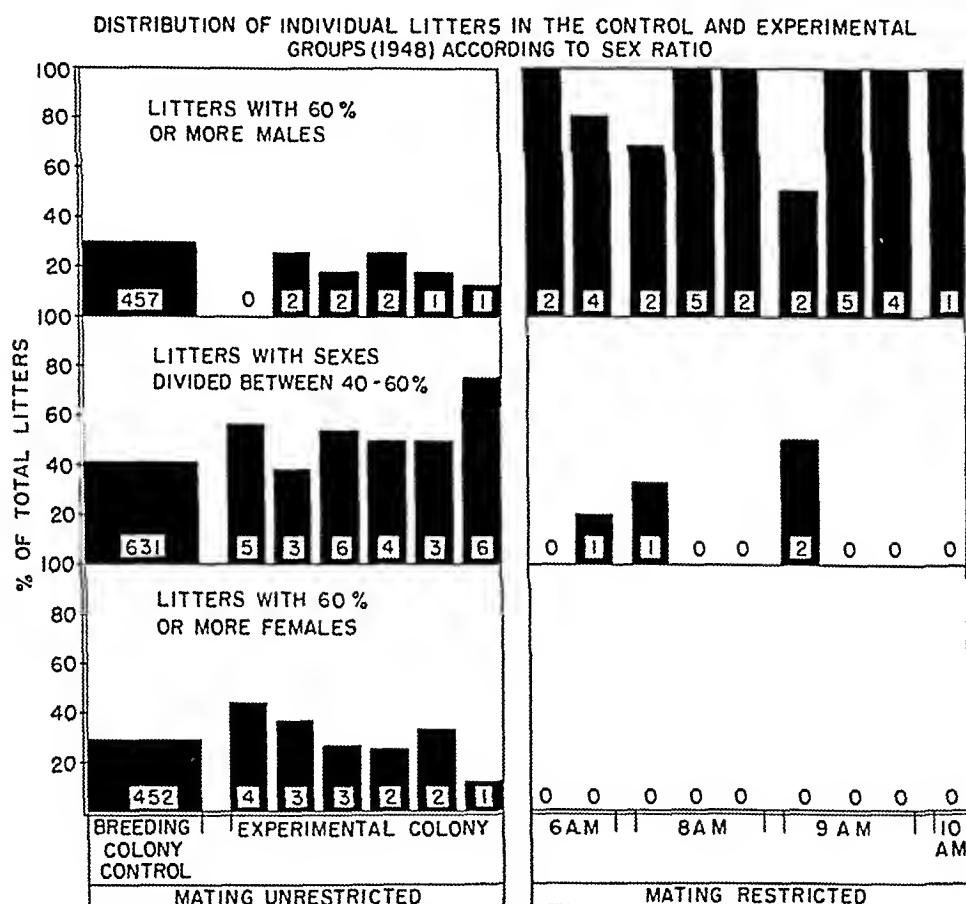


FIG 12—The breeding colony control group shows essentially equal distribution of the predominantly female and the predominantly male litters (Fig 1). The experimental colony control, using a relative surplus of males as compared with the small number of females in heat at a given time, shows a somewhat greater percentage of litters having a female preponderance as compared with those having a male preponderance. As contrasted to these, in the delayed-insemination groups, not a single litter showed a preponderance of females, only four showed a relatively equal distribution of sexes, while all other litters showed a preponderance of 60 per cent or more males.

females) and 10,700 (5,417 males and 5,283 females) offspring have reached the age of 21 days, with a sex ratio of 102.49 and 102.54 males per 100 females for the respective years.

In order to make the matings in the experiments as normal as possible, and to minimize handling, we have utilized the reports as given by Blandau and others^{10, 11} that the majority of female rats go into heat between 5 and 10 P M,

with the peak occurring at 7 o'clock (see Figs 9 and 13) The length of heat as given by them averaged 13.7 hours and ovulation was complete in almost all animals by the tenth hour after the onset of heat (Fig 13)

With these facts in mind and in order to produce pregnancies late in the fertility period, the first experiments in delayed insemination were carried out at 3, 6, and 9 A M The results, as shown in Figure 10, reveal that in the first three experiments the most striking variation in the sex ratio obtained was in the 6 A M group Since only a few experiments could be run because of the small size of the colony, it was decided to limit the experiments to the 6 A M

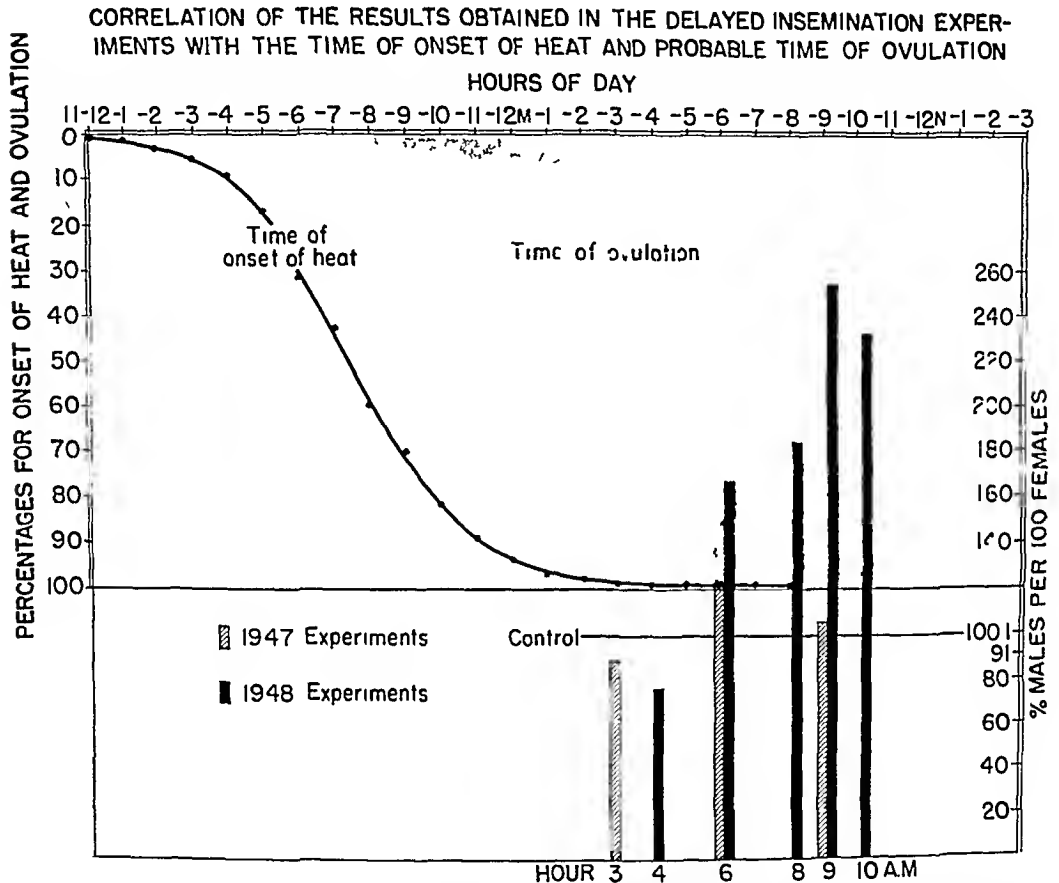


FIG 13—In order to show the relationship between the time of insemination and ovulation, we have plotted our experimental results of delayed-insemination superimposed on a graph (plotted from the published figures of Blandau, *et al*) showing the time of onset of heat and the probable time of ovulation in the rat. This shows that with insemination performed at progressively increasing periods of time following ovulation, there is a corresponding increase in the percentage of male offspring. The controls here are the 100 per cent line for the breeding colony sex ratio and the 91 per cent line for the experimental colony control as used throughout these experiments.

group to see if the preponderance of males would be maintained. This was found to be true. The almost equal sex ratio in the 9 A M group statistically is of little significance, it was felt that faulty equipment allowed insemination earlier than recorded on the chart. This will be explained later. Further check on the 9 A M matings was left for the 1948 experiments, our objective at this

time being to determine whether or not the experiment warranted continued investigation. In the 10 experiments carried out in the 6 A M group there were 458 offspring with a ratio of 149 males per 100 females as compared with 100 males per 100 females in the control group. This gave a 49 per cent increase in the percentage of males.

1948 EXPERIMENTS

Early in 1948 many of the unsatisfactory physical conditions in the laboratory were remedied. Among these was the institution of accurately controlled hours of light (from 6 A M to 8 P M) and darkness (from 8 P M to 6 A M). Our objective was to determine how late in the heat period a reasonable number of pregnancies could be obtained, and the time at which there would be the highest percentage of males. We began the experiments using the hours 4 and 6 A M which we believed to be near the probable time of ovulation. The 4 A M group compared roughly with the 3 A M group of 1947 while the 6 A M group with 67 offspring gave a ratio of 168 males per 100 females as compared with 149 males per 100 females in the 1947 experiments.

TABLE IV—*Effect of Late Insemination on the Sex Ratio of Individual Litters (Rat)*

Time Late Insemination	Female Preponderance		Sexes Equally Divided		Male Preponderance			
	75-100%	60-75%	40-60%		60-75%		75-100%	
			No	%	No	%	No	%
6 A M	0	0	1	14.3	6	85.7	0	0
8 A M	0	0	1	10	8	80	1	10
9 A M	0	0	2	15.4	4	30.8	7	53.8
10 A M	0	0	0	0	1	100.0	0	0

We then began further experiments utilizing later hours as given in Figure 11B. In the 8 A M group with 90 offspring the ratio of males per 100 females was increased to 190 while in the 9 A M group with 103 offspring, this ratio was further increased to 255 (Figure 11B, for individual litters and a statistical chart of these see Table V and Fig. 12). In the first 10 A M experiment only one pregnancy resulted. In all likelihood this rat went into heat late, since at this time all other rats in the group apparently had passed through the heat period, further experiments in this group have not as yet been carried out. In this one litter (7 males and 3 females) the sex ratio was 233 males per 100 females.

In addition to the control figures taken from the medical school breeding colony of rats, we considered it necessary to run an additional control, using the same groups of animals under identical conditions as in the late insemination experiments, except for the fact that the males and females were together continuously for the duration of the experiment (Fig. 11A). Each group of rats used once for a control experiment, was used both before and after this time for late insemination experiments. In six control groups there were 481 offspring. The ratio of males per 100 females varied from 74 to 107, with an average of 91 (Fig. 11A).

TABLE V—*All Experiments with Late Inseminations and Their Controls for the Year 1948 Using Constant Periods of Light and Darkness*

Exp No	Mating Permitted Beginning at	Dates Mating Permitted	Day of Delivery	No per Litter		Total No per Exp		% Males per 100 Females
				M	F	M	F	
1	4 A M	Feb 5–Feb 25	Mar 11	3	3	3	3	100
2	4 A M	Mar 10–Mar 30	April 6	3	5	3	5	60
1	6 A M	Feb 7–Feb 27	Mar 18 Mar 22	8 5	3 2	13	5	260
2	6 A M	April 27–May 17	May 20 May 20 May 20 May 22 May 24	7 7 4 5 6	4 3 2 7 4	29	20	145
1	8 A M	Feb 14–Mar 5	Mar 23 Mar 28 Mar 28	4 5 8	4 2 2	17	8	215
2	8 A M	April 6–April 26	April 28 May 11	7 6	3 4	13	7	185 7
3	8 A M	July 26–Aug 15	Aug 19 Aug 26 Aug 30 Sept 1 Sept 4	6 6 7 4 6	4 3 4 2 3	29	16	181 2
1	9 A M	April 13–May 3	May 16 May 16 May 16 May 20	5 7 8 8	2 3 2 3	29	10	290
2	9 A M	July 26–Aug 15	Aug 24 Aug 26 Aug 30 Aug 30	5 5 5 6	4 4 1 2	21	11	191
3	9 A M	Aug 14–Sept. 3	Sept 4 Sept 8 Sept 16 Sept 16 Sept 21	2 6 7 6 3	0 3 3 2 0	24	8	300
1	10 A M	July 26–Aug 15	Aug 25	7	3	7	3	233 3
1	Controls unlimited	April 23–May 13	May 16 May 16 May 20 May 23 May 24 May 25 May 26 May 26 May 26	5 7 3 4 6 6 2 5 4	7 5 7 6 5 8 5 6 8	42	57	73 7
2	Controls unlimited	April 23–May 13	May 18 May 19 May 20 May 22 May 22 May 22 May 22 May 24 May 27	6 4 3 5 7 6 3 4 4	5 7 6 4 3 2 4 8	38	39	97 4

TABLE V—(Continued)

Exp No	Mating Permitted Beginning at	Dates Mating Permitted	Day of Delivery	No per Litter		Total No per Exp		% Males per 100 Females
				M	F	M	F	
3	Controls unlimited	April 23–May 13	May 16	6	7			
			May 16	8	7			
			May 16	6	5			
			May 20	8	5			
			May 20	6	5			
			May 22	5	7			
			May 22	6	4			
			May 24	2	6			
			May 27	3	7			
			May 31	4	6			
			June 1	6	5	65	64	101.6
4	Controls unlimited	May 17–June 7	June 8	3	3			
			June 9	4	5			
			June 9	5	4			
			June 11	3	6			
			June 15	6	4			
			June 15	3	1			
			June 15	2	5			
			June 23	4	5	30	33	90.9
5	Controls unlimited	May 24–June 14	June 15	5	4			
			June 16	4	3			
			June 16	5	3			
			June 16	3	3			
			June 19	2	4			
			June 20	3	4			
			June 20	6	5			
			June 28	3	3	31	29	107
6	Controls unlimited	June 7–June 27	June 30	2	5			
			July 1	4	3			
			July 3	3	3			
			July 3	6	4			
			July 7	2	4			
			July 14	4	5			
			July 19	2	9	23	30	76.7

It is also of interest to compare the sex ratio of individual litters in these 1948 late insemination experiments and in the controls (Fig 12). In the breeding-colony control group and in the controls in the experimental colony, from 40 to 60 per cent of the litters were approximately evenly divided, from 20 to 30 per cent of the litters showed 60 per cent or more females and another 20 to 30 per cent showed 60 per cent or more males. In the late insemination experiments there was no litter with as many as 60 per cent females, only four litters were relatively equally divided, while the great preponderance of litters (27) showed from 60 to 100 per cent males (Fig 12).

DISCUSSION

These experiments as carried out were based on the knowledge that the great majority of rats go into heat within a period of a relatively few hours, and that for most rats ovulation follows within from 7 to 10 hours^{10, 11}. Although there is considerable variation in the onset of heat and the time of ovulation (Fig 13), these variables were not excluded under the conditions in which

these experiments had to be carried out, and therefore they are reflected in the results obtained. Furthermore, although the time when the males and females were put together was accurately controlled, the actual time of mating following this might have been variable*. However, by taking advantage of the times when the great majority of the rats went into heat and when they ovulated, statistically significant data have been obtained. The fact that rats that went into heat and also ovulated at hours different from the majority were not eliminated makes the results more, rather than less, highly significant. In order to demonstrate graphically these variations as to time of onset of heat and the subsequent time of ovulation, we have plotted the graph relating to the onset of heat and the time of ovulation from reports made by Blandau and his co-workers^{10, 11}. The graph giving the time of onset of heat shows that 10 per cent of the rats had gone into heat by 5 P M and that another 18 per cent did not go into heat until after 10 P M, while only an occasional animal went into heat at any one hour from that time until the following noon (Figs 9 and 13). The preponderance of ovulation (88 per cent) occurred within the period of from 7 to 10 hours after the onset of heat, leaving approximately 12 per cent in which ovulation occurred later than 10 hours, but with ovulation in all complete at 13 hours (Fig 13). The results of our 1947 and 1948 experiments with late insemination are plotted on this same chart showing the preponderance of males where mating was first permitted at 6, 8, 9 and 10 A M. This shows the relationship between the time of insemination in these experiments and the probable time of onset of heat and subsequent ovulation. The resultant deviation of the sex ratio from the average, with the high percentage of males in practically all litters (Tables IV, V and Fig 12) brought about by simply postponing mating from the presumed normal time until the times indicated in the experiments, is very obvious.

Because of the small size of the colony, the animals could not be sacrificed to determine the sex of all embryos. Each litter was sexed as soon as feasible following birth, but at times there was some delay, and certain fetuses born dead may have been destroyed by the mother. These conditions, however, prevailed in both the control and delayed-insemination groups.

In plotting the curve in Figure I to demonstrate this pattern of variation in the sex ratio, only the more accurately controlled 1948 experiments were used. The total offspring in the 6, 8, 9 and 10 A M experiments were used and the percentage of males and females for each hour determined. From a base line of zero the percentages of males were charted below and the percentages of females above, as indicated by the solid lines.

* In one of the 1947 experiments the door separating the males from the females opened prematurely because of defective equipment and mating may have occurred earlier than planned. This experiment was eliminated. This premature opening resulted from the jarring loose of the trap door by the hyperactivity of the highly excited rats. Such may have happened in other experiments during this year, since the cages were not routinely inspected during the night and such an error may have accounted for the low ratio of males to females in some of the experiments. However, such premature mating would not detract from, but would add to, the significance of the over-all data obtained.

It is our opinion that in most animals there is a broad band in the heat period during which time mating most frequently occurs, with a resulting relatively equal sex ratio. As an evolutionary process, the maximal mating response would come to lie in the period resulting in the sex ratio optimum for the propagation of the species. In the midportion of the graph (Fig. 1) we have left such a theoretical area clear. Since there is a preponderance of males in the later stages of the heat period, and since the control figures in our 1st breeding colony shows practically an even distribution between males and females there must be some time in the fertility period when insemination results in a preponderance of females to counterbalance the preponderance of males resulting from inseminations occurring late in the heat period. We have assumed this to be in the earliest stages of the fertility period. In order to plot a graph for this, giving a total sex ratio of approximately equal distribution of sexes, we have reversed the percentages of males and females for the 6, 8, 9 and 10 A.M. experiments and placed them in the earliest hours of the fertility period, as shown by the dotted lines in Figure 1. Furthermore, although the female, as shown by the copulatory response, may go into heat early in the evening, there may be a lag in the time of mating, as compared with the earliest period of fertility, due either to the time required for the female to reach her maximum receptivity or to the amount of stimulation required to build up the mating response in the male, or both. Consequently, under normal conditions, probably only a relatively small percentage of inseminations occur during the earliest stages of the fertility period. In the late stages of the fertility period, mating is also probably relatively infrequent, in part because of the declining receptivity of the female, and in part because of the diminishing aggressiveness of the male. The small number of pregnancies per unit of rats obtained in our late mating experiments may give some corroboration of this.

In order to see how the sex ratios of an individual litter in a normal breeding colony might fit in with such a concept, we have analyzed every litter in the breeding colony for one year. There were 12,135 offspring in 1,540 litters, with the sexes equally divided (6,071 males to 6,064 females). The litters were grouped according to the sex ratio, and the results in percentages of the whole were plotted on the lower part of Figure 1, extending throughout the heat period. It was found that the groups of litters containing from 75 to 100 per cent males or females were each 9.3 per cent of the total number, the groups of litters containing from 60 to 75 per cent of males or females were likewise almost identical in size, comprising 20.3 per cent and 20 per cent of the total, respectively. The large midgroup of litters with the sexes approximately equally divided (from 40 to 60 per cent ratio) formed 41 per cent of the total.

It is interesting to speculate as to how such a curve of distribution of sexes, dependent on the time relationship of insemination to ovulation, might work toward balancing the distribution of offspring for the best propagation of the species. Under conditions giving a preponderance of males in the species,

they would become more aggressive and mate earlier in the heat period, with a resultant increase in the female offspring. On the other hand, with an increasing depletion of the male population, an increasing number of matings would probably occur in the later stages of the heat period, with a resultant increase in the number of male offspring.

It is interesting to speculate as to how the time of insemination in relation to ovulation could affect the sex of the offspring. Theoretically, with the passage of time during the fertility period, there might be a change in

- 1 The permeability of the ovum
- 2 The viability and aggressiveness of the extrachromosome spermatozoa
- 3 The motility of the extrachromosome or female producing spermatozoa as compared with the male producing spermatozoa
- 4 Genital-tract conditions

It is entirely theoretical but to us it seems easiest to explain the effect of the time factor on the sex of the offspring on the basis of the relative differences in motility, viability and aggressiveness of the two types of spermatozoa.

PROPOSED EXPERIMENTS

Further experiments now contemplated will be directed toward the control of some of the variables accepted in these experiments, at the same time confirming more accurately the results already obtained with larger series of offspring. This will necessitate accurate determination of the onset of heat in each female and an accurate record of the time of insemination, thereby giving us control of two of the most important three variables, leaving uncontrolled the time of ovulation.

Simultaneously experiments are to be carried out to give inseminations at the earliest possible time in the fertility period to determine whether or not this will increase the percentage of females in the sex ratio. In order to give the highest degree of accuracy, it is contemplated that the animals in all these experiments will be sacrificed just prior to the termination of pregnancy, and the sex of each fetus determined by microdissection.

As soon as satisfactory facilities can be provided, we plan to undertake similar experiments in other laboratory animals, and particularly in cattle.

We also feel that the time has arrived to apply to humans, in selected cases, the information so far obtained. Preparations for this are already under way.

We hope that eventually experiments can be carried out directed toward determining why this variation in the sex ratio occurs.

SUMMARY

1 In experimental breeding of rats we have increased the percentage of male offspring as compared with the female from a normal of 100:1 to percentages varying from 149 to 255. This was accomplished by delaying insemination until varying hours after the expected time of ovulation, the greater the time interval after ovulation, the greater was the percentage of males.

2 An analysis of more than 65,000 pairs of dizygotic twins reveals in each year's group approximately 27 per cent more like-sexed than unlike-sexed.

pairs On the basis of our experimental studies, we feel that this constant surplus, inconsistent with chance alone, results from inseminations occurring both early and late in the fertility period

CONCLUSIONS

On the basis of our experimental studies and a statistical analysis of large numbers of human twins, it is our opinion that the time factor between insemination and ovulation directly influences the sex of the offspring

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THE TREATMENT OF CONGENITAL ATRESIA OF THE ESOPHAGUS WITH TRACHEO-ESOPHAGEAL FISTULA*

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CONGENITAL ATRESIA of the esophagus with tracheo-esophageal fistula was well described by Thomas Gibson¹ of London in 1703, yet in 1918, 215 years later, Plass² was able to find only 136 completely verified cases recorded in the literature. This suggests that the anomaly is an unusual one, but the number of cases observed during recent years proves this assumption to be incorrect. Gray Turner³ stated that congenital atresia of the esophagus occurs once in approximately 2,500 births, or with about the same frequency as harelip and cleft palate. Turner's statement is supported by the fact that 89 such cases were admitted to the Boston Children's Hospital in a seven-year period. Congenital esophageal atresia may occur either with or without a fistulous communication with the trachea. A fistula may connect the trachea with either the proximal or the distal esophageal segments, and rarely with both esophageal segments. Vogt's⁴ classification of the varieties of congenital atresia of the esophagus is the one most often used and is quite satisfactory. He divided them into three main types (Fig 1)

- I Agenesis of the esophagus
- II Atresia of the esophagus, no communication with the trachea
- III Atresia of the esophagus, fistulous communication with the trachea or (rarely) with one of the main bronchi
 - (a) Fistula between the proximal segment of the esophagus and the trachea. Proximal end of the distal segment ends blindly at about the level of the bifurcation of the trachea.
 - (b) Proximal segment ends in blind pouch, distal segment communicates with the trachea or rarely with one of the main bronchi (Fig 2)
 - (c) Both proximal and distal esophageal segments communicate with the trachea.

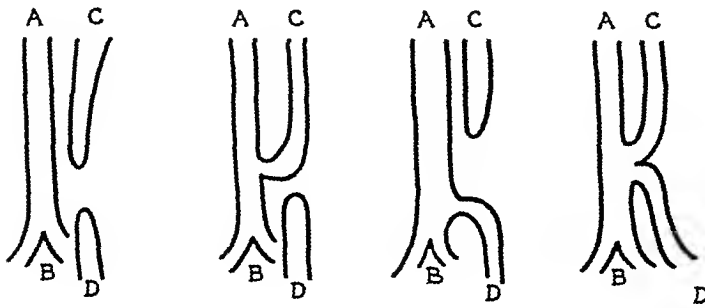
Occasionally tracheo-esophageal fistula occurs in the absence of esophageal atresia.

The variations of this anomaly are of more than academic interest to the surgeon, for the type of operation to be done, even the approach, depends upon the nature of the lesion. An attempt should therefore be made to determine the exact anatomic relationship between the esophageal segments and between each segment and the trachea.

The question of diagnosis will be considered only in so far as it affects treatment. The diagnosis of congenital atresia of the esophagus may be made

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CONGENITAL ATRESIA OF THE ESOPHAGUS



- A - TRACHEA
- B - BIFURCATION OF TRACHEA
- C - UPPER SEGMENT OF ESOPHAGUS
- D - LOWER SEGMENT OF ESOPHAGUS

FIG 1—Congenital atresia of the esophagus. Illustrating the relationships which may exist between the esophageal segments and the trachea. In addition, complete agenesis of the esophagus may occur and, rarely, tracheo-esophageal fistula in the absence of esophageal atresia.

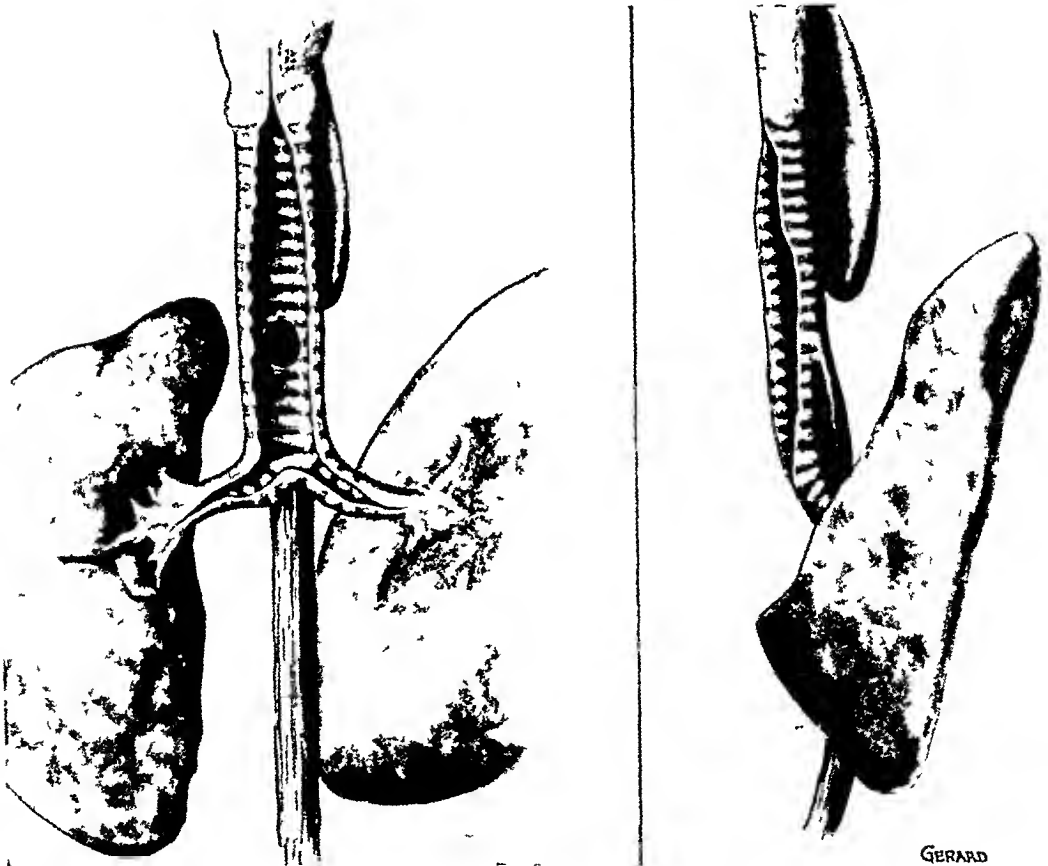


FIG 2—Congenital atresia of the esophagus with fistula between the distal segment of the esophagus and the trachea, Type 3b, the one most frequently encountered.

with a considerable degree of certainty on the basis of the history of excessive drooling of saliva and the immediate regurgitation of everything given by mouth, with strangling. In infants with esophageal atresia a soft-rubber catheter passed into the esophagus will meet an obstruction from 10 to 12 cm from the gum margin. If along with such an obstruction there is evidence of gas in the stomach and intestines, there is almost certainly an associated tracheo-esophageal fistula. However, a marked stenosis of the esophagus without



FIG 3—Roentgenogram showing the wide distribution of barium in the bronchial tree as the result of use of this material to outline the upper esophageal segment

agenesis of the distal esophagus, which, of course, eliminates the possibility of esophageal anastomosis. When reconstruction of the esophagus is not possible, one should consider the advisability of doing a primary esophagogastrostomy, which can best be done through a left transpleural approach. Direct anastomosis of the esophageal segments, on the other hand, is more easily and more safely accomplished through a right extrapleural approach.

Even when a fistula is known to be present, one cannot be certain whether or not a direct anastomosis is feasible without knowing the length of the

fistula may give the same findings. A definite diagnosis can be made by roentgenoscopic and roentgenographic examinations following the injection of iodized oil into the upper esophagus. Barium should never be used for this purpose, for if it is regurgitated and aspirated into the tracheobronchial tree it produces obstruction of many of the smaller bronchi and leads to serious respiratory difficulties (Fig 3). If it is shown that the upper esophageal segment ends blindly, air in the stomach and intestines can only mean there is a fistula between the distal segment of the esophagus and the trachea or one of the main bronchi. If the upper esophageal segment ends blindly and there is no air in the stomach and intestines, it is usually assumed that there is no fistulous communication between the esophagus and the trachea, but Haight⁵ has shown that this is an unjustifiable assumption since he has demonstrated small fistulas under such circumstances. Atresia without fistula may mean there is

proximal segment and the level at which the distal segment joins the trachea. If the proximal segment is short and the distal segment joins the trachea at or near the carina, it is unlikely that a satisfactory anastomosis will be possible (Fig 4). It is therefore apparent that one should attempt to determine whether or not there is a fistula and the distance between the two segments when there is a fistula. Haight has stressed the importance of roentgenoscopic examination after the injection of iodized oil as a means of gaining a more accurate idea of the length of the proximal segment, for its position varies considerably with inspiration and expiration. The information obtained from roentgenograms may therefore be misleading.



FIG 4—(A, Left) Upper blind esophageal pouch extends to the level of the fourth rib posteriorly. Anastomosis is readily done. (B, Right) Very short upper esophageal segment. Direct anastomosis was not possible.

Byron⁶ recommends tracheoscopy when there is doubt as to the presence of a fistula. This may be the most accurate way of demonstrating a small fistula, but even the slight trauma incident to the passage of a rigid tube through the larynx may produce sufficient edema to necessitate tracheotomy. It seems likely that a small fistula can be demonstrated more safely by roentgenograms made after iodized oil is injected into the trachea as well as into the esophagus. The preliminary application of a small quantity of 2 per cent procaine to the tracheal mucosa will control the cough reflex sufficiently to permit slightly warm oil to be used satisfactorily. The tracheal injection should be made while the infant is held in the dorsal recumbent position, with the upper part of the body slightly elevated. By this means the level of the fistula may be accurately determined and the distance between the esophageal segments made known preoperatively.

A roentgenogram should be made of the chest and abdomen before any opaque material is injected. The type and extent of pulmonary involvement is thereby demonstrated. The abdomen is included on the roentgenograms because the amount and distribution of air in the stomach and intestines may be significant. A large amount of air in the stomach and little in the intestines would suggest pyloric stenosis and air in the stomach and no air distal to the stomach would point to duodenal atresia.

Foster and Shaw⁷ reported the postmortem findings in a child with esophageal atresia who died on the eighth day. A typical hypertrophic pyloric stenosis was also discovered. Careful search should always be made for associated anomalies, for they occur frequently. In 94 infants with esophageal atresia, Plass found evidence of 59 associated anomalies, in 24 of these there was atresia of the anus.

TREATMENT

The treatment of congenital atresia of the esophagus was altogether unsuccessful until within the last decade. In fact, the condition appeared so hopeless that little thought seems to have been given to its treatment until the early part of this century. The attitude of the surgical profession was well stated in 1869 by Mr. T. Holmes,⁸ a London surgeon and the author of a treatise on pediatric surgery. He said: "The evidence, then, which we at present possess discourages the hope that this malformation is remediable by operation, since in all the cases which are on record, the obliteration has extended so far down that the lower portion of the tube could not have been reached by a surgical operation. In cases where a tracheal fistula exists in connection with obliteration of the esophagus, it may be questioned whether life would be permanently maintained even if the passage of food could be restored, and in any such case the attempt ought not, I think, to be made. But in cases where no such communication can be made out, I cannot see any objection to the operation, if the parents wish it, after the almost inevitably fatal nature of the case has been explained to them. The object would be, to cut down upon the point of a catheter passed down the pharynx, and then to attempt to trace the obliterated esophagus down the front of the spine, until its lower dilated portion is found. A gum-catheter would then be passed through an opening made in the upper portion, and so into the stomach through the lower portion. If the two portions are near enough to be connected by silver sutures over the catheter, and if the latter can be retained until they have united, permanent success might possibly be obtained."

Mr. Holmes' attitude was understandably pessimistic, but he did suggest the possibility of end-to-end suture of the esophageal segments and was probably the first surgeon to give serious consideration to that possibility. The attitude expressed by Brennemann⁹ of Chicago in 1918 was still far from optimistic, even though some progress had been made toward the development of a rational operative treatment of this anomaly, as his statement indicates. He said: "The ultimate ideal of all surgical attempts would be this union of the

upper and lower portions of the esophagus. It is of interest in this connection that these commonly meet at the same level. Hoffman attempted this operation, approaching it, however, by the impossible neck route. He gave it up and did a simple gastrostomy with the inevitable result. Whether this operation will ever be possible the future advances of intrathoracic surgery must decide. Even if possible, it would still seem probable that pediatric limitations will form an insurmountable barrier. In these otherwise hopeless cases, however, one gives the surgeon a full rein with a clear conscience."

Up to that time gastrostomy was the operation most frequently done in connection with this anomaly but, as indicated by Brennemann, it was altogether futile. In 1904 Villemain¹⁰ passed a gastrostomy tube through the pylorus and around into the first part of the jejunum, in the hope that he might thus avoid the regurgitation of food and its aspiration through the fistula into the tracheobronchial tree, but the result was no better than with simple gastrostomy.

Richter¹¹ of Chicago apparently was the first surgeon to appreciate the primary importance of closing the tracheo-esophageal fistula and was also the first one who had the temerity to make a direct transthoracic approach to the fistula. He entered the mediastinum and closed the fistula in two infants, both died, but his report served to direct attention to closure of the fistula as well as to the establishment of esophageal continuity, which he advocated but did not attempt.

Lanman¹² of Boston performed the first end-to-end suture of the esophageal segments in 1936 and in 1940 made an excellent report of the experience of the surgeons at the Boston Children's Hospital, where 32 infants with congenital atresia of the esophagus had been observed. Thirty of them had been operated upon, four had direct anastomosis of the esophageal segments. All died, but in spite of the results Lanman insisted that end-to-end suture was the procedure of choice in suitable cases and predicted that success would soon be reported. The following year Cameron Haight¹³ of Ann Arbor performed a successful direct anastomosis which was reported in 1943. Previous to this (in 1939) Logan Leven¹⁴ of St. Paul and W. E. Ladd¹⁵ of Boston had each had patients survive multiple-stage procedures, closure of the fistula, gastrostomy and cervical implantation of the proximal esophageal segment.

It was clear, however, that primary anastomosis of the esophageal segments was far preferable to any of the less direct, multiple-stage procedures and many surgeons felt that it should be used even if it resulted in a somewhat higher mortality. There can be little doubt that the final result is far superior to that achieved by the use of any other type of operation, and now that Haight, Swenson¹⁶ and many others have shown that primary anastomosis can be done with a reasonably low mortality, there should be no question that it is the procedure to employ when it is feasible.

Singleton¹⁷ and Lyons¹⁸ have expressed a preference for the transpleural approach to the esophagus, but Haight and Swenson, and in fact a majority of surgeons working in this field, prefer the extrapleural approach when it appears that primary esophageal anastomosis will be possible. We believe that

the right posterior extrapleural approach is safer and better in those cases of congenital atresia of the esophagus with tracheo-esophageal fistula in which the roentgenoscopic and roentgenographic findings indicate that a satisfactory approximation of the two esophageal segments may be obtained

During the past year we have used the following plan of management and have so far been reasonably well satisfied with the majority of the measures we have employed. However, some changes are indicated

PREOPERATIVE MANAGEMENT

Upon admission to the hospital the child is examined and an attempt is made to discover the type of anomaly present and whether or not there are associated anomalies, especially those which might complicate the immediate picture or those apt to be incompatible with life. When an atresia with associated tracheal fistula is found, the child is placed in the prone position and the foot of the crib is elevated. This position is maintained for a considerable part of the time, but we have followed Haight's suggestion and have turned the child from the prone to the lateral positions at intervals, usually with the right side dependent. Haight suggested this maneuver with the idea that if atelectasis developed it would be likely to occur in the dependent lung, and atelectasis of the right lung would not prevent operation through that side. We believe this should be modified to this extent. If the findings indicate that a direct anastomosis will be feasible, the right side should be kept dependent a considerable portion of the time, but if it is apparent that a direct anastomosis cannot be done, the left side should be kept dependent since it is likely that a left transpleural approach will be used. Mucus and excess saliva are removed at frequent intervals by gentle suction. We have not employed continuous suction for this purpose.

Infants with this anomaly are usually greatly dehydrated, so fluid is administered in relatively large amounts as equal parts of Hartman's solution and 5 per cent glucose in water, or as 3 per cent glucose in water. It is important to avoid giving too large quantities of electrolytes because of the danger that they will be retained and will thereby lead to generalized edema. We believe, however, that the very pronounced edema sometimes seen postoperatively is primarily due to increased pressure within the mediastinum, the result of leakage and infection. In one case in which there was unusually marked edema, large collections of air and purulent fluid were evacuated by opening the mediastinum. This was followed by very rapid disappearance of the edema.

We have given blood freely and, although we have usually limited each transfusion to the traditional 10 cc per pound, we have not hesitated to give a sufficient total amount to raise the hemoglobin to 20 Gm or even higher. Penicillin is given in moderate dosage preoperatively and in large dosage postoperatively from 20 to 25 thousand units every three hours. The preoperative penicillin is important as an aid in preventing pulmonary complications. Streptomycin is usually given for the first few days after operation to help combat infection by those organisms little affected by penicillin.

OPERATIVE PROCEDURES

In those patients with an associated fistula we have done a preliminary gastrostomy, usually within the first 24 hours after admission (Fig 5) We have done the gastrostomy preliminary to thoracotomy primarily for the purpose of deflating the stomach and intestines, which in a large percentage of the cases are markedly distended Such distension makes the anesthetist's problem much more difficult and thereby adds to the seriousness of the undertaking We have also noted an occurrence which has been commented upon by Richter, Daniel¹⁹ and others, even if there is no pronounced preoperative distention, it will become marked if the anesthetic is administered under

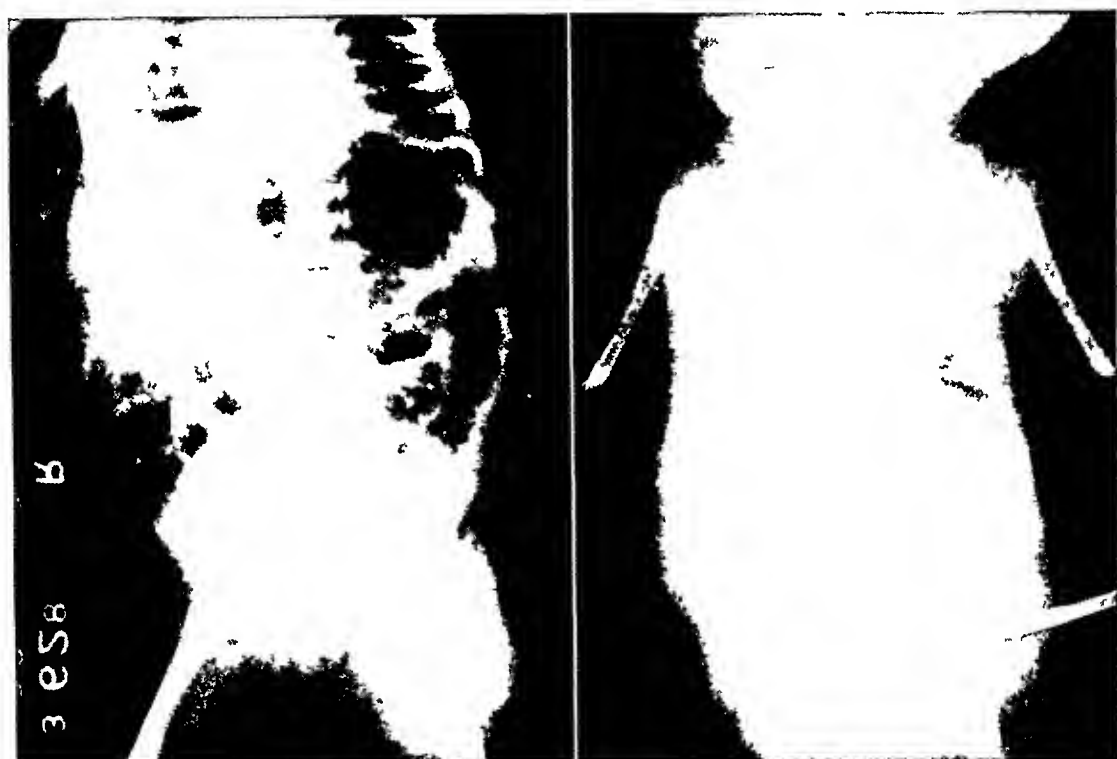


FIG 5—Rapid deflation of stomach and intestines following gastrostomy The fistula had not been closed

positive pressure We believe our results have justified this change in the order of procedure, but we now realize that it is unwise to do a preliminary gastrostomy unless the findings indicate that a primary anastomosis is possible In two instances we have done the preliminary gastrostomy, and have then made a right-sided extrapleural approach only to find that the segments were so widely separated it was not possible to approximate them

In three cases we passed the gastrostomy tube through the pylorus and around into the jejunum with the idea that this might help prevent regurgitation This maneuver had been used by Villemain and by Logan Levin, but we were unaware of this at the time we used it During manipulation of the tube through the pylorus, that structure was visualized and palpated and was normal in all three cases Interestingly enough, all three of the infants on

whom this procedure was tried were in the hospital at the same time, all were females and all developed hypertrophic pyloric stenosis. We performed the Fredet-Rammstedt procedure on two of them and both made uneventful recoveries. One was about to be operated upon when she showed improvement and went on to recovery without the aid of surgery. The clinical and roentgen findings leave little doubt that she too had hypertrophic pyloric stenosis.

We agree with Haight that general anesthesia is necessary to obtain the desired degree of relaxation for the thoracotomy, but we use local anesthesia for the gastrostomy. For the thoracotomy we use ether and oxygen administered through a small, snugly fitting mask. We have hesitated to use an intratracheal tube because of the fear of its producing edema of the glottis, and we



FIG 6—Incision for right extrapleural exposure of the esophageal segments when direct anastomosis seems feasible

have not felt that it offered sufficient advantage, when the extrapleural approach is used, to justify that risk. When the transpleural route is used, an intratracheal tube offers far greater advantages.

The infant is placed on the operating table in the prone position, but with the right side slightly elevated and with the right arm carried well above the head (Fig 6). A slightly curved incision is made at the level of the fifth rib, starting about 2 cm. to the right of the spine and extending well beyond the posterior axillary line. The trapezius and rhomboid muscles are divided and a narrow segment of the dorsal border of the latissimus dorsi muscle is usually cut. The scapula is retracted upwards with the attached muscles to expose the fourth rib, which is resected subperiosteally from the spine to near the mid axilla. The head of the rib is disarticulated. The internal periosteum of the fourth rib is carefully incised but the incision is discontinued at least 0.5 cm.

short of the lateral cut end of the rib. This measure and disarticulation of the head of the rib are used to avoid laceration of the pleura on the cut ends of the rib. Only one rib is resected and no others are divided because we have found that we can obtain altogether adequate exposure in this way. Furthermore, the mobilization of the chest wall resulting from resection of four or five ribs must cause some interference with respiration in the postoperative period, when respiratory difficulties are so apt to occur from other causes. Also it seems likely that some degree of permanent deformity will result from the posterior division of so many ribs in such young individuals.

The parietal pleura is separated from the chest wall above and below the level of the fourth rib and from the mediastinal structures by careful finger

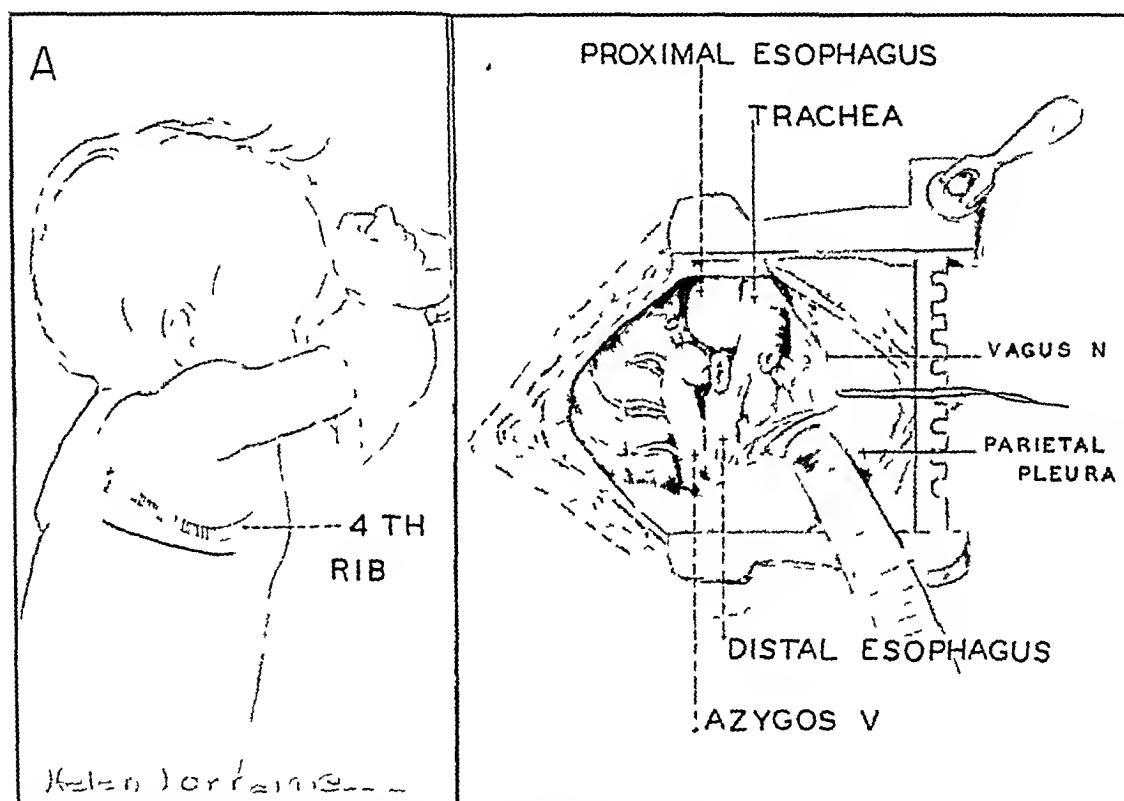


FIG 7—Note the excellent exposure obtained by resecting only one rib (the fourth)

dissection, pressure being directed against the chest wall or mediastinal structures and not against the thin pleura (Fig 7). The azygos vein is divided between fine silk ligatures, and an attempt is then made to find the distal segment of the esophagus, for we believe the fistula should be closed before the proximal segment is investigated. Finding the distal segment is usually not difficult, but may give some trouble if the esophagus joins the trachea at the carina. The esophagus is ligated with fine silk as near as possible to the trachea, a mosquito clamp is applied about 0.5 cm distal to the ligature and the esophagus is divided against the clamp by a sharp knife. The cut ends are treated with phenol and alcohol and attention is then turned to the proximal segment.

When the upper segment has been exposed, a traction suture is inserted in its distal portion and it is dissected free well up into the neck. A traction suture is then inserted into the distal segment and the clamp is removed. The tip of the proximal segment may be either incised or excised. If the segments are sufficiently long, we prefer using Haight's method of telescoping the small distal segment into the upper segment (Fig 8). If there is any tension when we attempt to telescope the ends, we do a simple end-to-end suture with two rows of interrupted sutures of fine silk (Fig 9).

When the anastomosis has been completed, a small (10 or 12 French) catheter, with several openings near the tip, is inserted through a puncture wound in an interspace well below the incision and is fixed near, but not in

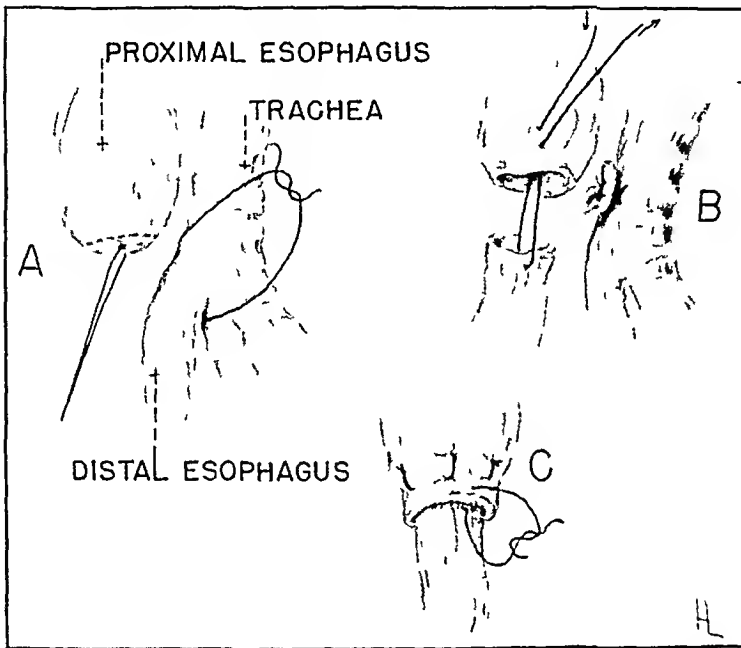


FIG 8—Illustrating closure of the fistula and anastomosis by telescoping the smaller distal esophageal segment into the wider proximal segment (Haight). Note the vertical application of the sutures.

contact with, the anastomosis by a suture of 0000 plain catgut. The catheter is connected for under-water drainage. Muscles and fascia are approximated with widely spaced, loosely tied, interrupted sutures and the skin is closed with interrupted sutures of 0000 plain catgut. A gauze dressing is used for 24 hours, then removed and the incision is covered with collodion.

The drainage tube is removed in seven or eight days if there is no leakage from the esophageal suture line. If there is leakage, the tube is left in until the fistula heals.

In those cases of atresia with agenesis of the distal segment or those in which the two segments are too widely separated for primary anastomosis, one may make a left transpleural approach and do a primary esophagogastrostomy,

as has been done by Swenson, Lyons and Byion. Swenson's patient recovered, the others died, but death was due to causes other than the operation in both instances.

Singleton tried to bring widely separated esophageal segments together by incising the diaphragm at the hiatus and elevating the cardia but was unsuccessful. He apparently did not divide the left gastric artery, and it would seem that this would be necessary before the cardia could be elevated sufficiently to be of appreciable help. Division of the left gastric artery should be near its origin from the celiac artery and care should be taken to avoid injury to the vascular arches connecting it with the other gastric arteries, otherwise the

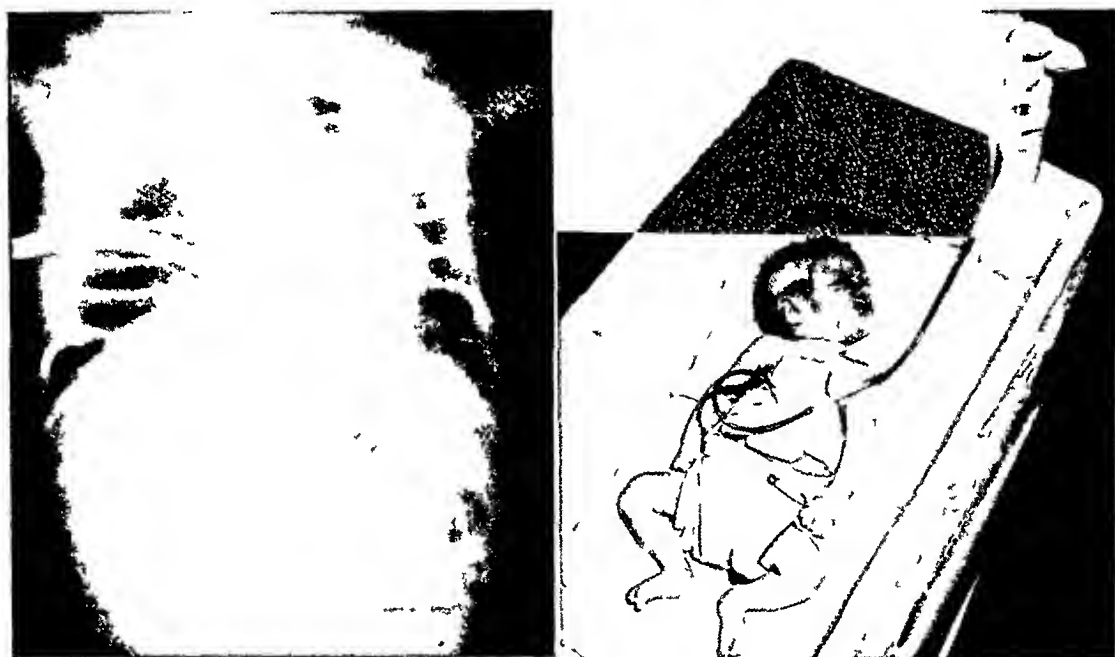


FIG 9 (Left) —Roentgenogram following the instillation of iodized oil into the esophagus two weeks after anastomosis by telescoping the distal segment into the proximal segment. Note the very slight narrowing. The small amount of oil in the bronchi is the result of regurgitation and aspiration and is not due to recurrent fistula. The tube extends into the jejunum.

FIG 10 (Right) —Postoperative use of the gastrostomy tube, which is connected to the barrel of the asepto syringe, thus is fastened well above the infant's body level. It is used for feeding and is left open between feedings to permit escape of gas, thereby diminishing the danger of regurgitation.

blood supply to the esophagus might be compromised. Either of the procedures described above is preferable to any of the multiple-stage operations, but they are extensive, and if the infant's general condition is not good, it may be wiser to adopt one of the stage procedures, such as closure of the fistula, gastrostomy, and cervical implantation of the upper segment. Later the operation used by Sweet²⁰ or that described by Reinhoff²¹ may be used to establish continuity of the alimentary tract. The operation described by Reinhoff is remarkably safe but, of course, is by no means ideal.

SUMMARY OF OUR CASES

From 1941 to 1948, we had operated upon 11 infants with congenital atresia of the esophagus with tracheo-esophageal fistula. In four of them, the fistula was closed and the esophageal segments were anastomosed. A gastrostomy was done for temporary feeding. Two recovered from the operation, but in both cases there was severe infection and leakage from the suture line. One infant recovered and is developing satisfactorily, but has an esophageal stricture which requires occasional dilatation. The other child developed a tight stricture and a recurrent fistula between the trachea and esophagus. A secondary operation was performed when the child was about seven months of age. All of the mediastinal structures were encased in dense scar, but the fistula was closed and the esophagus sutured. The child's condition was satisfactory for the first two days, but leakage then occurred at the suture line, the drainage tube became obstructed and the child died from a tension pneumothorax.

One child developed very marked edema of the entire body, including the larynx. An emergency tracheotomy was done, and following this there was progressive improvement for several weeks. At the end of six weeks the child seemed ready to leave the hospital and the parents were so notified. That night she was found dead in her crib. Autopsy was not permitted.

The fourth child died on the fourth postoperative day from a severe infection in the mediastinum.

In three cases the fistula was closed and end-to-end suture done. A tube was passed through the anastomosis into the stomach and left in place for temporary feeding. Gastrostomy was not done. One of these infants died shortly after being returned to the ward, apparently from shock. Both of the others developed severe infection in the mediastinum, leakage at the suture line and recurrent fistulas, one died on the fifth day and the other on the eighth postoperative day.

In three other children, the fistula was closed, but they were in such poor general condition, anastomosis was not attempted. The segments were tacked together in the hope that anastomosis would be possible at a later date. Both had gastrostomy for temporary feeding. All died within a few days. Two had widespread bronchopneumonia, one of these also had infection in the mediastinum. The third had a perforation of the distal esophageal segment, probably due to some injury at the time of operation.

The eleventh case showed only a small amount of air in the stomach and intestines, and at operation the lumen of the distal segment was so small it could not be used for anastomosis so the fistula was closed, and cervical esophagostomy and gastrostomy were done. The child died the following day, and autopsy was not permitted.

Of the 11 patients in this group, 8 died during the early postoperative period, 1 from shock, 2 from pneumonia and 4 from mediastinal infection. One child died 24 hours after operation, with cause of death undetermined. One infant died several weeks after operation at a time when it appeared to be making altogether satisfactory progress, with cause of death undetermined.

Two survived the primary operation, but one of these died following closure of a recurrent fistula. Only one of the eleven is now alive and well.

During the past year we have operated upon seven infants with congenital atresia of the esophagus and with tracheo-esophageal fistula. In all seven, gastrostomy was done one or two days preliminary to thoracotomy, and the gastrostomy tube was used to deflate the stomach and intestines. Because of this there was decided improvement in the ease of administration of the anesthetic, and in every instance the infant left the operating room in good condition. In five of them the esophageal segments were of sufficient length to permit satisfactory anastomosis. In four the distal segment was telescoped into the proximal segment and fixed with two rows of fine silk sutures. In one of them there was very slight leakage from the suture line for a few days. The leakage apparently developed about one week after operation and there was no evidence of infection.

In the other case a simple end-to-end suture was done, because the segments did not appear to be long enough to permit invagination or telescoping of the ends.

The only complications of importance occurred in three infants in whom the gastrostomy tube was passed through the pylorus and around into the jejunum (Fig 10).

COMMENT

In each instance the pylorus was normal at the time the gastrostomy tube was inserted. Leven²² has had two instances of hypertrophic pyloric stenosis in male infants operated upon for esophageal atresia and Swenson has had one such case. Foster and Shaw found hypertrophic pyloric stenosis at postmortem examination on an eight-day-old male infant, which died from an untreated atresia of the esophagus with tracheal fistula. However, there is no evidence to suggest that the two lesions are often associated.

Two of the infants operated upon during 1948 had short proximal esophageal segments and in both of them the distal segment joined the trachea at the carina. It was therefore not possible to anastomose the esophagus in either case. The fistula was closed and a cervical esophagostomy was done. Both made uneventful recoveries. Nine months later a modified Reinhoff operation was done in one of them. The old gastrostomy incision was excised and the gastrostomy was closed. The incision was extended upwards in the midline to the lower anterior chest wall. The xiphoid process was excised and the diaphragm split back for about 3 cm. The gastrohepatic and gastocolic omenta were divided at a sufficient distance from the stomach to avoid injury to the collateral vascular loops, and the main stem of the left gastric artery was divided between silk ligatures. The esophageal hiatus was then enlarged, the esophagus liberated above the cardia, doubly ligated and divided, and the distal stump inverted into the stomach with mattress sutures of silk. A subcutaneous tunnel was established from the upper end of the abdominal incision to the level of the cervical esophageal stoma, where an end-to-side anastomosis was made between the cervical esophagus and the fundus of the stomach. The child made an excel-

lent recovery, except for the development of a fistula at the site of anastomosis, which has not yet closed

The second child was operated upon only three weeks ago and will not have the esophagogastrostomy done for several months

COMMENT

Had the low junction between the distal esophagus and the trachea been demonstrated preoperatively in these two cases, we probably would have made a left transpleural approach. With such an approach the stomach could have been transplanted into the thorax for primary anastomosis with the proximal segment of the esophagus, or the esophageal hiatus could have been enlarged, the left gastric artery divided and an attempt made to elevate the cardia sufficiently to permit primary esophageal anastomosis.

Of the seven infants with congenital atresia of the esophagus and tracheo-esophageal fistula operated upon during 1948, five had direct esophageal anastomoses. Four healed without incident, one developed a transient fistula. The other two infants showed such wide separation of the esophageal segments that direct anastomosis was not possible and since the right extrapleural approach had been made, multiple-stage procedures were resorted to.

SUMMARY

Complete anatomic diagnosis is necessary in infants with congenital atresia of the esophagus, otherwise the treatment cannot be intelligently planned and executed.

Methods are discussed by which complete diagnosis may be made.

A plan of management is outlined, including certain details of operative technic, under which satisfactory results have been obtained in a small group of infants with congenital atresia of the esophagus and tracheo-esophageal fistula. Certain changes are suggested.

Eleven infants were operated upon prior to the adoption of our present plan of management. Only two of the 11 survived and one of these two died at seven months of age following an operation for the repair of a recurrent tracheo-esophageal fistula.

Seven infants operated upon during 1948 have all recovered. There are no doubt a number of factors responsible for the decided improvement in the results obtained in this latter group. The use of both penicillin and streptomycin for the prevention and control of infection has unquestionably been of primary importance.

It is believed, however, that certain other measures, especially the use of gastrostomy as a means of deflating the stomach and intestines before and during the intrathoracic operation, have been of some importance.

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ESOPHAGEAL RESECTION WITH END-TO-END ANASTOMOSIS EXPERIMENTAL AND CLINICAL OBSERVATIONS*†

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THE PURPOSE OF THIS PAPER is to present our experimental observations on partial resection of the thoracic esophagus with restoration of continuity by end-to-end anastomosis and to describe its application in two cases of inoperable carcinoma of the esophagus in an attempt to restore the ability to swallow

Because of the magnitude of esophagogastric anastomosis with transposition of the stomach into the thorax or neck, it occurred to us that restoration of the act of swallowing might be accomplished by such a lesser operation in those cases of carcinoma of the esophagus in which the primary tumor is resectable but in which it is impossible to eradicate all the carcinoma because of adjacent or distant spread. If the ability to swallow could be restored by such an operation, the superiority of this technic over roentgenotherapy or dilatations of the esophagus or gastrostomy, as other methods of palliation, would be readily apparent.

A conversation with Swenson about 10 months ago encouraged us in our efforts in this direction, for he stated that he thought the prevalent ideas regarding the vulnerability of the esophagus were not true and added that he had been able to perform in experimental animals resections of large portions of the thoracic esophagus with end-to-end anastomosis followed by recovery.

Swenson and Clatworthy¹ performed in 1947 experiments similar to those we were attempting and had also treated successfully a case of benign stricture of the esophagus by resection of the stricture with end-to-end anastomosis. And since then, another case of successful resection of an esophageal stricture with end-to-end anastomosis has been reported by Gross.² An account of our own experimental work follows.

EXPERIMENTAL OBSERVATIONS

Partial resection of the lower half of the thoracic esophagus with restoration of continuity by end-to-end anastomosis was performed on 21 dogs. The length of the esophagus resected varied from 4 cm to 7 cm. The average length resected was 5 cm. Since the average length of the thoracic esophagus of the dogs used in this series was 15 cm, this represented a resection of approximately 33 per cent.

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ESOPHAGEAL RESECTION

The operations were done under intravenous Nembutal anesthesia, and atmospheric air under positive pressure was delivered in an intermittent flow through an endotracheal tube while the pleural cavity was open. They were performed through a left thoracotomy incision in 11 animals and through a right thoracotomy incision in 10 animals. The approach was posterolateral, entering the pleural cavity through the fifth or sixth interspace without rib section or resection. The ribs were spread slowly and widely. The lung was allowed to collapse. On exposure of the lateral surface of the esophagus, two silk sutures were placed a known distance apart, varying from 4 cm. to 7 cm., to indicate the exact length of the segment to be resected (Fig 1).

In 12 of the 21 animals, the entire thoracic esophagus was then dissected completely from its mediastinal bed from the level of the diaphragm to the



FIG 1

FIG 2

FIG 3

FIG 1—The lateral surface of the esophagus is exposed in the depth of the wound, after retraction of the right lung anteriorly. The upper silk suture has been placed. One of the vagus nerves is coursing downward from left to right.

FIG 2—After freeing the thoracic esophagus from the diaphragm to the clavicles, its lower half can be delivered easily up to the level of the rib cage. The length of the segment between the upper and the lower spaced sutures is explained by the great elasticity of the esophagus.

FIG 3—The proximal and distal ends of the esophagus, at the left and right respectively, have retracted and are held in the tape ligatures. The excised segment, showing the spaced sutures, has shrunk slightly.

level of the clavicles (Fig 2). The marked segment of the esophagus was then resected after the application of heavy tape ligatures proximally and distally to prevent the escape of any esophageal contents into the mediastinum (Fig 3). After resection of the segment, traction was applied to the tapes to approximate the proximal and distal ends of the esophagus and the ends of the tapes were grasped in forceps to maintain the approximation. The ends of the esophagus were then anastomosed with a double layer of interrupted cotton sutures. Approximately 18 sutures were placed in each hemicircumference of the mucosa (Fig 4). In general, the knots were tied on the outside. No attempt was made to invert or evert the edges of the mucosa. They were merely approximated. Following suture of the mucosa, the edges of the muscularis were approximated. Approximately half as many sutures were used

in this layer. No attempt was made to suture the muscularis layer leak-proof (Fig 5).

Following the anastomosis, the tape ligatures were removed. During the procedure, injury to the vagus nerves was avoided as much as possible. No attempt was made to close the mediastinum. The pleural cavity was not drained. The lung was expanded. The thoracotomy wound was closed in layers with interrupted cotton sutures. Following operation, thoracentesis was performed on the operative side to remove any residual trapped air.

In nine of the 21 animals, the technic was the same except that the esophagus was not freed from the surrounding tissues beyond that portion which was to be resected.

In only two of the 21 animals was there considered to be a significant degree of tension on the sutures after anastomosis. In 17 of the 21, the dia-



FIG 4



FIG 5

FIG 4—The ends of the esophagus are shown approximated by traction on and fixation of the tape ligatures. The posterior layer of mucosal sutures has been placed. The posterior layer of sutures in the muscular layer are placed after rotation of the esophagus.

FIG 5—The completed anastomosis. After removal of the tape ligatures, the esophagus still has great mobility and is not stretched taut.

phragm was not paralyzed. In the two cases mentioned above, and in two others, all four in the group in which only the segment of the esophagus to be resected was freed, the phrenic nerve was crushed on the side of the operation (three left and one right).

In the group of nine animals in which only the segment of esophagus to be resected was completely isolated, it was necessary to sacrifice two or three recognizable arteries. In the other group of 12 animals in which the entire thoracic esophagus was freed from its bed, as many as seven arteries were sacrificed. Even in this latter group, it is noteworthy that bleeding occurred

frequently from the suture line after completion of the anastomosis and removal of the tape ligatures

The results of the operations are classified in two ways and are as follows

Among 11 dogs in which the resection was done through the left side, seven survived and four died

In 10 dogs in which the resection was carried out on the right side, seven survived and three died

Of 12 dogs in which the esophagus was completely freed from its bed in the mediastinum, eight survived and four died

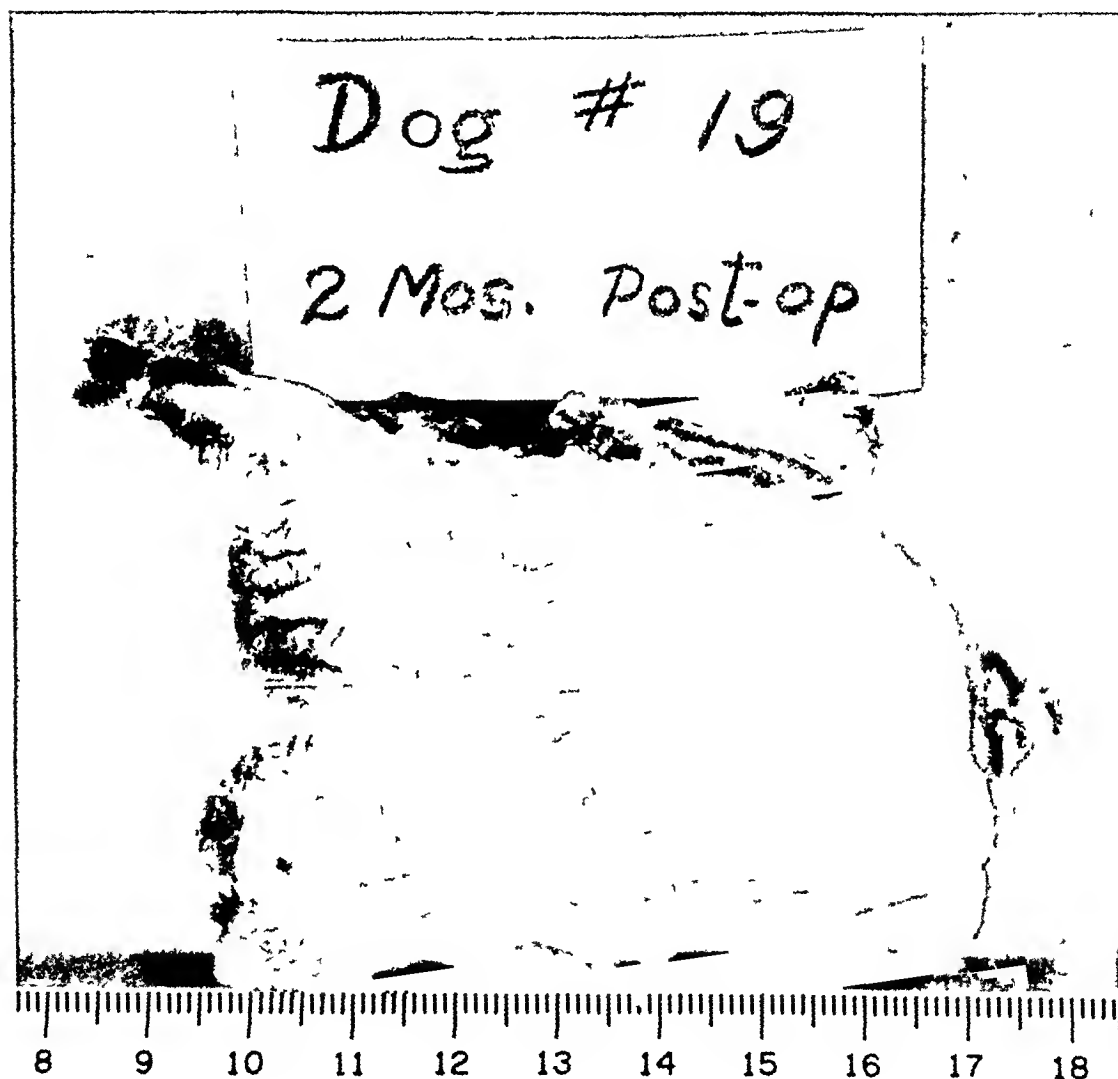


FIG 6—The wide epithelialized scar and the serrations of the edges of the proximal and distal normal mucosae are shown. There is a rim of gastric mucosa at the left.

In nine dogs in which only the segment to be resected was freed from its bed in the mediastinum, six survived and three died

Thus, the average mortality rate for both the side of operation and the technic of operation was approximately 33 per cent

In view of the high mortality, it must be noted that no therapy of any kind was given preoperatively or postoperatively, except that food and water were

withheld for seven hours before operation. In particular, no attempt was made to carry out replacement of any fluid or blood loss and no chemotherapy or antibiotic therapy was given at any time. Following operation, the animals were given access to water through the third postoperative day. Beginning on the fourth postoperative day, they were given the regular kennel rations.

In six of the seven animals that died following the operation, death occurred between the second and the tenth postoperative day. The average duration of life was four days. The cause of death in the six animals was bilateral empyema due to esophagopleural fistula resulting from failure to heal, the cause of this failure could not be ascertained. Certainly in some, tension on the suture line may have been a factor. In two of the six, there were one or more leaks through the suture line. In the other four, there was complete disruption of the suture line, with separation of the proximal and distal ends of the esophagus for distances varying from 1 to 3 cm. In five of the six animals, the blood supply in both ends of the esophagus appeared to be intact. In the other one, the distal end of the esophagus was viable, but the proximal end showed necrosis for the terminal 1.5 cm. The seventh dog that died following the operation died on the 30th postoperative day. At autopsy, except for extreme malnutrition, there was no apparent cause of death. The suture line was intact and there was no stricture. It is significant that in only one of the seven animals to die, and of the entire series of 21, was there any evidence of interference with the blood supply to the ends of the esophagus.

The surviving 14 animals were sacrificed at intervals of from two weeks to eight months following operation. All but one were in a good to excellent state of nutrition. Both pleural cavities were entirely normal except that, in about half the animals the lung was adherent to the thoracotomy scar, and in a few, it was also adherent to the region of the anastomosis. There was moderate fibrosis in the mediastinum in only four of the animals. The esophagus, on gross examination, was essentially normal externally in all except four animals, in which there was slight dilatation above the level of the anastomosis. In the others, the site of scar was difficult to recognize. The vagus nerves were scarred and were adherent to the region of the anastomosis in all specimens. There was no instance of gastric dilatation. On opening the esophagus, we found that the level of the anastomotic scar above the cardia varied from 2 to 6 cm, the average being 3 cm. In four of the specimens, the scar was about 1 cm in width. In these four, serrations could be seen in the edges of the normal mucosa where the sutures had cut through the mucosa, apparently as a result of tension on the suture line with stretching of the scar (Fig 6). Except for the scar, the mucosal surfaces appeared normal (Fig 7) in all except one specimen. In only one of the 14 specimens was there a slight stricture at the site of the scar (Fig 8). This occurred in one of the four specimens showing proximal dilatation. The specimen of the one animal in a very poor nutritional state showed a total esophagitis with several small ulcerations.

The length of the segment of the esophagus resected did not appear to bear any relation to recovery or death. There appeared to be no relationship between

the length of the resected segment and the width of the anastomotic scar. Also, there appeared to be no relationship between the width of the anastomotic scar and the extent of the dissection of the esophagus prior to resection and anastomosis.

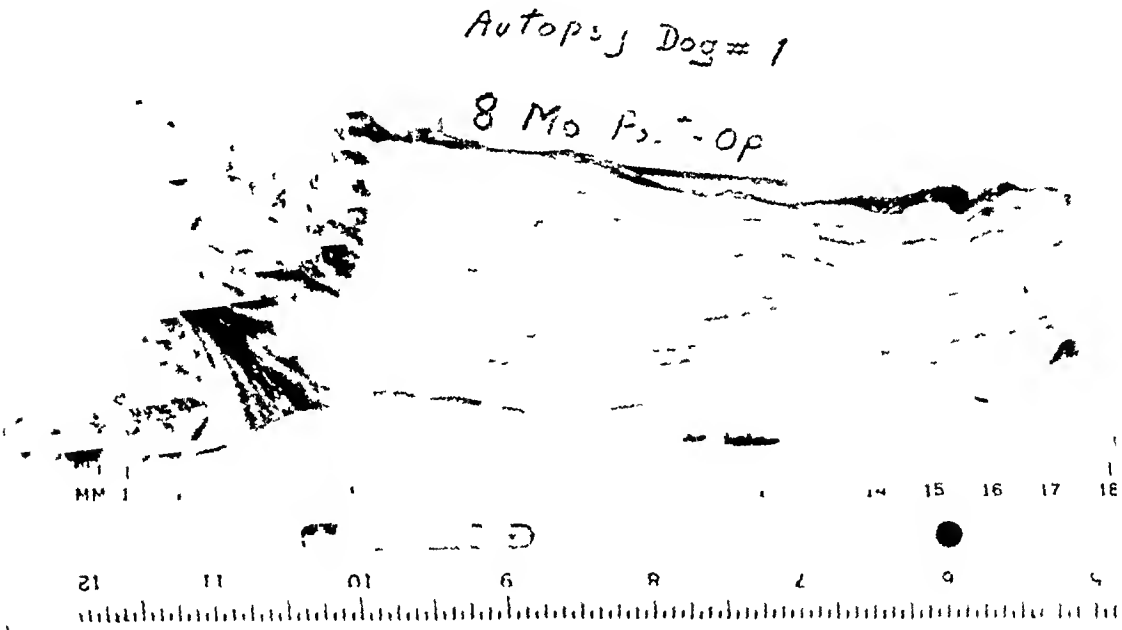


FIG 7—Photograph of a fresh specimen showing the typical appearance of the esophagus in the sacrificed animals. While more apparent in the gross, the anastomotic scar barely shows. Gastric mucosa is on the left.

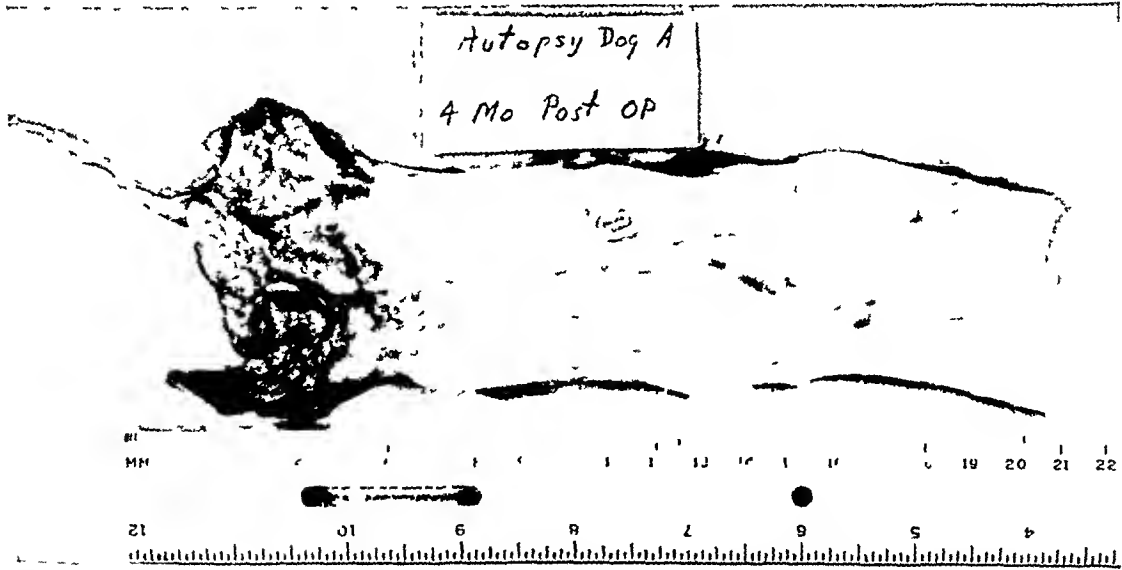


FIG 8—The photograph of the specimen presenting a slight stricture due to the anastomotic scar. The gastric mucosa is on the left.

Therefore, it may be said that in the dog, resection of from 30 to 35 per cent of the total length of the thoracic esophagus can be accomplished successfully in a high percentage of cases without any adjunctive therapy whatsoever. Since our experiments were done wholly on the lower half, further investigation

would be needed to determine the applicability of our findings to the upper thoracic esophagus and to the cervical esophagus

CLINICAL OBSERVATIONS

Case Report (Roper Hospital No 65241) —L G W, a Negro male, age 45 years, was admitted on February 16, 1948. The history was given by his wife. Nine years before his admission, he had noticed a sensation of a "jump in his chest" substernally. This persisted without change for the next eight years. One year prior to admission he began to have progressively increasing dysphagia due to a sense of obstruction. Two months



FIG 9 (Case 1) Photograph of the patient supported by an attendant, on the day following admission



FIG 10 (Case 1) Photograph of the initial esophagogram, demonstrating the filling defect in the lower third and the small esophageal hiatus hernia

before admission he started regurgitating his food. Three weeks before admission he became bedridden and unable to swallow even water. During the three weeks before admission, he had had no form of nourishment and no bowel movement.

The past history was noncontributory.

On physical examination the patient's temperature was 97.4° F, pulse 96, and respiration 24. The blood pressure was 40/0. He was moribund and extremely emaciated (Fig 9). There was no cervical lymphadenopathy. The trachea was in the midline. The heart and lungs were normal. The liver was not palpable. The remainder of the examination was noncontributory.

Red blood count 7,030,000. Hemoglobin 18 Gm. White blood count 12,500. Differential normal. Urinalysis normal. Total serum proteins 9.01 Gm per cent. Serum

albumin 6.07 Gm per cent Serum globulin 2.94 Gm per cent Blood Wassermann and Kline negative

Roentgenograms of the chest were normal. Roentgen examination of the esophagus, using barium, showed a constriction in the lower thoracic portion (Fig 10). There was moderate dilatation of the esophagus proximally. Most of the barium was regurgitated but a small amount entered the stomach, during the examination of which a small esophageal hiatus hernia was found.

Upon admission, the patient was started on intravenous fluid, electrolyte, amino acid, vitamin, and whole-blood therapy. His condition improved slowly so that by the sixth day after admission he had become normally alert and the blood pressure had risen slowly to 110/78.

On February 23, 1948, a jejunostomy was performed under local anesthesia. At operation, there was no evidence of intra-abdominal metastasis. Feedings by jejunostomy were begun the day after operation, at which time intravenous therapy was discontinued. Improvement in the state of his nutrition followed and he began to have normal bowel movements. His weight was 109 pounds, which represented a gain over the weight on admission.

On March 2, 1948, esophagoscopy was performed under sodium-pentothal anesthesia. An obstructing, granular lesion was found 36 cm beyond the alveolar margin. A biopsy showed epidermoid carcinoma (grade I—Broders), and confirmed the clinical diagnosis.

His general appearance and strength continued to improve until March 8, 1948, although on this date his weight was only 100 pounds.

Operation. On March 9, 1948, under nitrous-oxide induction and endotracheal ether anesthesia supplemented with curare, a left posterolateral thoracotomy was performed and the pleural cavity was entered in the seventh interspace without rib section or resection. The ribs were spread slowly and widely. The pleurae were normal and the lung was allowed to collapse. Excessive turbid brown fluid in the pleural cavity was aspirated. The inferior pulmonary ligament was markedly indurated but grossly it did not contain tumor. The lower esophagus was exposed. About 10 cm above the diaphragm a tumor mass was found in the esophagus. There was apparent invasion by the tumor of the pericardium anteriorly, of the pleura and lung to the right, and of the adventitia of the aorta to the left. The tumor involved a segment of the esophagus 6 cm in length. The segment of the esophagus containing the tumor and the adjacent adventitia of the aorta were dissected free from all surrounding tissues, leaving residual carcinoma in the pericardium and in the right pleura and lung.

In view of the fact that a curative resection could not be performed, it was decided to resect the segment of esophagus containing the tumor and to do an end-to-end anastomosis. Accordingly, the entire esophagus was dissected free, from the diaphragm well up into the neck. An incidental esophageal hiatus hernia was found, through which the stomach projected for a distance of about 4 cm above the diaphragm. The 6-cm segment of esophagus was resected. Anastomosis was effected without undue tension, the surgeon using separate layers of interrupted silk sutures in the mucosa and in the muscularis. The muscularis of the proximal end was badly torn in the dissection of the esophagus and its suture was tedious.

Upon completion of the anastomosis, a band of tissue at the esophageal hiatus extending from the diaphragm to the stomach was divided, allowing the stomach to herniate into the chest for an additional 1 cm. The left phrenic nerve was crushed at its reflection from the pericardium onto the diaphragm. Several small mediastinal lymph nodes were removed for examination. A transnasal Levine tube was passed down the esophagus into the stomach. An internal intercostal nerve injection using a 1 per cent Novocaine solution was made in the second through the tenth nerves. Catheters were brought out of the pleural cavity in the second interspace anteriorly and in the eighth interspace in the posterior axillary line for postoperative closed drainage of the pleural cavity. One hundred cc of saline containing 100,000 units of penicillin were instilled into the

pleural cavity The left lung was re-expanded The wound was closed in layers without drainage with interrupted silk sutures throughout

Bronchoscopy was performed following the operation to empty the tracheal-bronchial tree of any discharge Transfusions totaling 1,500 cc of blood were given during the operation The operating time was approximately four hours The patient's condition was satisfactory throughout

Pathologic examination of the segment of esophagus excised (Fig 11) showed epidermoid carcinoma (grade II—Broders) with lymphatic invasion and extensive penetration of the muscular layer The mediastinal lymph nodes were normal

Postoperative Course The patient's recovery was uneventful Immediately following operation both intercostal catheters were allowed to drain under water The temperature rose to a peak of 100.4° F on the first day following the operation It returned to normal on the third postoperative day and remained so throughout the rest of the patient's hospital stay The anterior and posterior intercostal catheters were

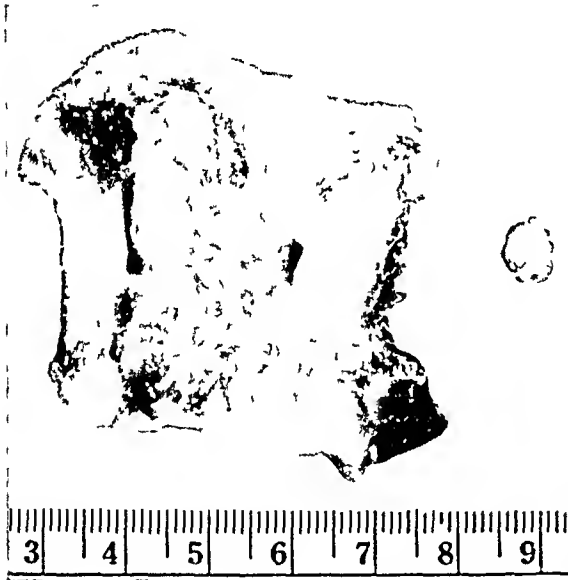


FIG 11 (Case 1) Photograph of the ulcerated mucosal surface of the excised segment of esophagus The rims of normal mucosa (at top and bottom) above and below the tumor are not wide Also shown is one of the mediastinal lymph nodes



FIG 12 (Case 1) Esophagogram in June, 1948, shortly after the return of dysphagia, showing a filling defect below the level of the arrow, due to recurrence of tumor

removed on the second and fifth postoperative days respectively There was moderate sanguineous discharge from both catheters The thoracotomy wound healed per primam The transnasal Levine tube was removed on the third postoperative day, the stomach having been kept empty by suction through the tube until this time Also on the third postoperative day, intravenous therapy was discontinued and jejunostomy feedings were resumed On the fifth postoperative day, the patient became ambulatory and remained so thereafter Penicillin therapy, begun 24 hours prior to operation, was discontinued on the eighth postoperative day For the first five postoperative days the patient was given injections of 100,000

units, and from the fifth through the eighth days, 50,000 units, each injection intramuscularly at three-hour intervals. Roentgenograms of the chest on the tenth postoperative day were normal.

On the fourth postoperative day the patient was allowed to have water by mouth and his swallowing was normal. Later it was learned that he had been eating without difficulty roasted peanuts brought to him by his wife since the day following operation. After taking water by mouth without difficulty, his diet was increased gradually. The jejunostomy feedings were continued throughout the postoperative period, but on discharge he was able to eat a soft diet and ground meat without any difficulty. He was discharged from the hospital on the 13th postoperative day. He refused to have roentgen examination of the esophagus prior to his discharge.

On April 13, 1948, his general appearance was excellent. His weight was 127 pounds. He ate slowly, but he could eat meat, rice, and peanuts in particular, and anything else desired. He had discontinued the use of the jejunostomy the week before and the wound was healed. He had not returned to work but planned to do so soon. A barium swallow showed no delay in the passage of barium into the stomach. However, there was again a filling defect of the esophagus in its lower third.

He was readmitted to the hospital for study on June 29, 1948. In the previous week or two he had begun to have some dysphagia. The physical examination was not remarkable. His weight was 124 pounds. The routine blood studies and urinalysis were normal. Roentgenograms of the chest were normal. Esophagoscopy was performed under pentothal anesthesia. At the 36-cm level, approximately at the site of anastomosis, the esophagus was narrowed by ulceration. The scope could not be passed through the area of narrowing. A biopsy was taken and showed epidermoid carcinoma of the esophagus. This proved that there was a local recurrence of the tumor. Also, esophagograms using iodized oil as the contrast medium were made. These showed an area of marked irregularity and constriction in the lower thoracic portion (Fig 12).

Thereafter, the patient had progressively increasing dysphagia and loss in weight and strength. He was admitted to the hospital for terminal care for a few days before his death on November 24, 1948. Autopsy confirmed again the diagnosis of carcinoma of the esophagus.

Case Report (Roper Hospital No 65065) R. L. C., a white female, age 46 years, was admitted on March 11, 1948. Progressively increasing dysphagia began in September, 1947. By Christmas, 1947, she was at times unable to swallow even liquids and regurgitation was frequent. She lost 44 pounds in weight. Since June, 1947, she had also a frequent, dry cough and some change in her voice. She had no pain at any time.

In 1940 she had a radical mastectomy on the left side for carcinoma of the breast without axillary or other known metastasis. Otherwise her past history was noncontributory.

On physical examination she did not appear sick. There was evidence of weight loss. The voice was hoarse. There was a large scar in the left pectoral and axillary regions. There was no evidence of local recurrence of the tumor of the breast. In direct laryngoscopic examination revealed a paralysis of the right vocal cord. Otherwise the physical examination was essentially normal.

The routine blood and urine studies and the serum protein determinations were normal.

Roentgenograms of the chest showed an increase in the pulmonary markings in the bases (Fig 13). Roentgen examination of the esophagus with barium indicated marked obstruction in the upper portion of the thoracic esophagus (Fig 14).

On esophagoscopy under local anesthesia, there was a marked stricture of the esophagus 23 cm beyond the alveolar margin, without apparent alteration of the mucosa. A biopsy showed normal mucosa.

The initial diagnosis was primary carcinoma of the esophagus, or secondary carcinoma of the esophagus metastatic from the breast. Exploratory thoracotomy was advised and preoperative therapy begun.

Operation On March 22, 1948, under endotracheal ether anesthesia, a right postero-lateral thoracotomy was performed through the fifth interspace without rib section or resection. The ribs were spread. The entire superior mediastinum was exposed by extrapleural dissection. In doing so, a small hole was torn in the parietal pleura and pneumothorax ensued. There was an apparent tumor mass in the esophagus just beneath and above the azygos vein. The tumor invaded the posterior wall of the vein. The segment of the esophagus containing the tumor was about 3 cm long. After division of the azygos vein and its tributaries between ligatures, the tumor was partly exposed. The tumor apparently invaded also the posterior wall of the trachea. After tedious dissection, it was entirely freed from the surrounding tissues. The entire posterior mediastinum was thickened, suggestive of tumor or fibrosis. The right subclavian artery seemed to be surrounded by tumor as it emerged from about the trachea. A biopsy was shaved from the posterior wall of the trachea just above the carina without opening its lumen. A frozen section of this showed carcinoma.



FIG 13



FIG 14

FIG 13 (Case 2) Roentgenogram of chest on patient's admission to the hospital, showing the abnormality in the base of the right lung

FIG 14 (Case 2) The initial esophagogram, showing a filling defect opposite the arrow

In view of the fact that the biopsy of the trachea showed tumor and that grossly there appeared to be certain tumor in the remainder of the mediastinum which could not be eradicated, it was decided to perform a resection of the esophagus containing the tumor and to restore the continuity by end-to-end anastomosis. Accordingly, the entire esophagus was then freed by finger dissection from the diaphragm well up into the neck. A section of the esophagus about 4 cm in length containing the tumor was excised. It was then noted that in the mucosa of the proximal esophagus there were two nodules. A biopsy of one of these was obtained and showed no carcinoma. End-to-end anastomosis between the ends of the esophagus was performed with an inner layer of interrupted silk sutures in the mucosa and an outer layer in the muscularis. The right diaphragm was paralyzed inadvertently by injury to the phrenic nerve. A drain was placed in the extrapleural space and brought out through a stab wound below the level of the incision. The right lung was re-expanded. The wound was closed in layers with interrupted

ESOPHAGEAL RESECTION

silk sutures Bronchoscopy was performed following operation to empty the tracheal-bronchial tree of any discharge The trachea was normal Blood transfusions totaling 1,500 cc were given during operation The operation was of five hours' duration The patient's condition throughout was satisfactory

Pathologic examination of the resected portion of the esophagus showed extensive infiltration of the wall of the esophagus by malignant tumor with only a small area of involvement of the mucosa (Fig 15) The tumor was epithelial in type, having definite glandular tendencies quite comparable to the carcinoma of the breast removed in 1940 The original breast sections were available for comparison

Postoperative course The woman's recovery was characterized by transient generalized edema, by dyspnea and cyanosis, evidence of bilateral bronchopneumonia and a



FIG 15 (Case 2) The mucosal surface of the excised segment of esophagus, containing metastatic carcinoma The margins of normal mucosa above and below the tumor are on the right and left



FIG 16 (Case 2) The esophagogram three weeks following operation shows moderate extravasation of barium at the level of anastomosis

frequent cough only partly effective She was given oxygen therapy Gradually, improvement occurred and the lungs became clear However, a low-grade fever persisted The wound healed per primam

She was allowed water by mouth on the sixth postoperative day and had no difficulty in swallowing On the seventh postoperative day she became ambulatory and was able to drink with ease over 2,000 cc of water Thereafter, she was given a soft diet and intravenous therapy was discontinued

On the eleventh postoperative day, roentgen examination of the esophagus with barium was made The esophagus at the level of the anastomosis was grossly irregular but showed no obstruction However, there was moderate extravasation of barium outside its lumen at this level Therefore, the patient was placed on nothing by mouth again and parenteral therapy was resumed until a gastrostomy was performed on April 5, 1948

Gastrostomy feedings were begun the next day. Repetition of the roentgen examination of the esophagus with barium on April 13, 1948, showed essentially the same findings (Fig 16).

For the week prior to April 14, 1948, the patient was afebrile, so penicillin, given preoperatively and postoperatively, was discontinued. But at this time, she began to have chills and fever and to vomit. A persistent cough became productive of pure yellow pus. There developed evidence suggestive of a lung abscess on the right. On April 17, 1948, she expectorated a silk suture in the sputum. A fistula between the esophagus and the trachea was suspected. On April 20, 1948, bronchoscopy was performed. There was an obvious perforation in the lower end of the trachea. The perforation was about 4 mm in diameter. Its edges were reddened and elevated. Following bronchoscopy, esophagograms were made with iodized oil, and the oil passed rapidly into the trachea and bronchi at the level of the esophageal anastomosis (Fig 17).

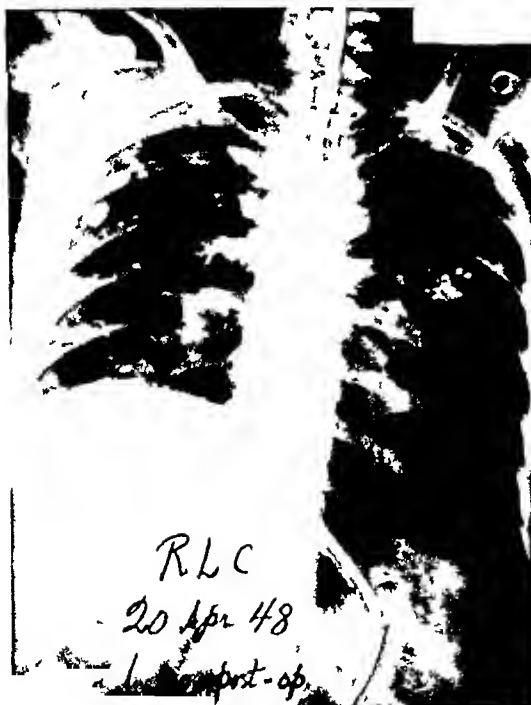


FIG 17

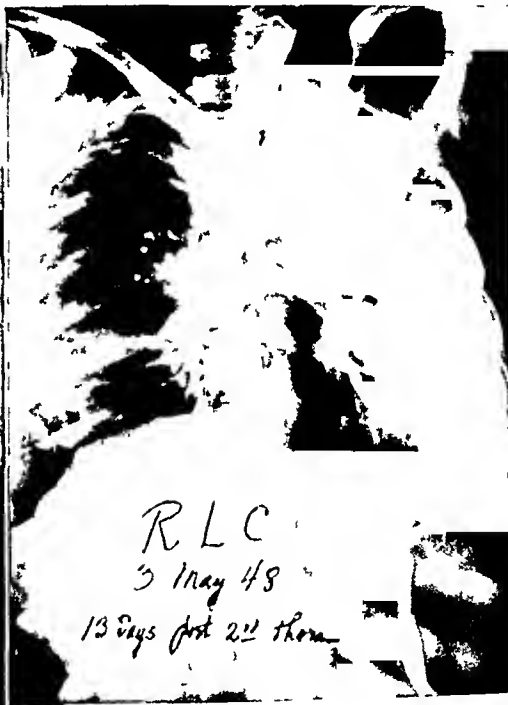


FIG 18

FIG 17 (Case 2) Lipiodol in the left lung is shown, following the injection of the esophagus through an upper and a lower transgastric catheter.

FIG 18 (Case 2) Esophagogram showing the upper esophagus filled with oil and the esophagus practically empty below the level of anastomosis. A large amount of oil has escaped into the tracheobronchial tree.

Operation Because of the esophagotracheal fistula, a second thoracotomy was performed on that day, April 20, 1948. Under endotracheal ether anesthesia, the same wound was reopened and the same extrapleural exposure obtained. There was no fluid in the extrapleural space. There was dense fibrosis or tumor throughout the mediastinum. In the lower end of the trachea a perforation about 4 mm in diameter was exposed. In trying to free the trachea, its posterior wall split open so that the perforation enlarged to a length of 2 cm. The posterior wall of the trachea at this level was markedly inflamed and friable. A biopsy was obtained and was reported later as showing only inflammatory tissue and no tumor. The esophagus was covered with a dense layer of fibrous tissue and was not definitely seen. No defect in it was seen. There was no abscess cavity in

the mediastinum. The edges of the defect in the trachea were such that repair by suture was considered impossible. The defect was plugged with several oxidized gelatin sponges. Nothing further was done. The right lung was re-expanded. Closed drainage of the extrapleural space was effected. The wound was closed. The patient's condition was fairly satisfactory at the end of the operation, during which she was given 1,000 cc of blood.

Postoperative Course It was expected that she would expire. But in spite of persisting fever, phlebitis in the right leg, signs of bilateral pulmonary infection, continued vomiting, and loss of an additional 20 pounds in weight since admission to the hospital, she recovered on oxygen and penicillin therapy. The lungs cleared, the wound healed per primam and she became ambulatory again. It was believed that the tracheal component of the fistula was closed temporarily, but esophagograms made on May 3, 1948, showed even greater passage of the radiopaque oil in the trachea and bronchi (Fig 18). Also there was a marked stricture at the site of the anastomosis.

On bronchoscopy five days later, the tracheal perforation was seen again. In view of the fact that at this time the patient was afebrile, that the lungs were clear again, and there was no chance of the fistula's closing spontaneously, another thoracotomy for excision of the esophagus and a further attempt to close the trachea were advised.

Operation On May 10, 1948, the third thoracotomy was performed. Under the same anesthesia and through the same wound, the sixth interspace was entered. The superior mediastinum was exposed extrapleurally. The esophageal anastomosis was found to be partly disrupted, with a fistula penetrating into the trachea. The proximal and distal ends of the esophagus were excised. The stump of the proximal esophagus was delivered onto the skin of the neck. The stump of the distal esophagus was closed by inversion. The defect in the posterior wall of the trachea was now 2 cm in diameter. A free graft of parietal pleura was sutured into it, and the whole covered with a layer of oxidized gelatin. This stopped the exchange of air for the time being. Closed drainage of the extrapleural space was effected. The lung was re-expanded and the wound closed.

On pathologic examination, the segments of the esophagus resected on either side of the anastomosis did not show residual carcinoma.

Postoperative Course The woman's recovery was characterized by varying degrees of dyspnea, cyanosis and wetness of the lungs. Air poured out of the intercostal catheters intermittently, indicating that the fistula in the trachea communicating with the extrapleural space was open at intervals. On May 17, 1948, on turning toward the left side, suddenly she became markedly dyspneic and cyanotic and died apparently by drowning.

Autopsy was performed. Incomplete expansion of the right lung was found with residual bloody fluid in the extra pleural space. This space communicated with a defect in the trachea which had failed to close, and it was apparent that the cause of death was drowning by the influx of the extrapleural fluid into the tracheobronchial tree. Gross examination of the body was not remarkable otherwise except for a marked acute inflammatory reaction in both lungs, confirmed by microscopic section. Microscopic sections of the trachea through the area of perforation showed extensive invasion of the wall by carcinoma. A small focus of metastatic carcinoma was also found in a mediastinal lymph node. In addition, the fibrofatty tissue in the superior mediastinum showed invasion by similar malignant tumor cells.

DISCUSSION

Although we have no direct proof, the experimental observations constitute indirect evidence that the arteries supplying the esophagus must have frequent anastomoses throughout the length of the thoracic esophagus. After complete severance of all arteries entering the esophagus from the thorax, the only known remaining sources of blood supply are the esophageal branches of the inferior thyroid entering the cervical portion and the branches of the left gastric

and phrenic entering the cardiac portion. Yet, in the 12 animals in which severance of the thoracic blood supply of the esophagus was effected, the remaining proximal and distal ends of the esophagus maintained their viability in all except one.

The belief that frequent anastomoses between the esophageal arteries exist throughout the thoracic esophagus is further supported by unpublished observations of the authors on the viability of the thoracic esophagus in a small series of dogs after complete severance of the thoracic blood supply without resection of an intervening segment. These experiments were undertaken before beginning the present study. The animals were sacrificed five days following operation. The esophagus, though ecchymotic, was viable throughout in each instance.

Further observations in support of the belief expressed above concern the viability of the esophagus after operations in which the blood supply, or at least a part of it, may be seriously impaired or disrupted. Such operations include those done to determine the operability of carcinoma or to repair esophageal hiatus hernia and congenital short esophagus, and esophagogastrostomy for cardiospasm. In such operations, part of the esophagus may be freed widely without fear of complications due to inadequate blood supply.

Since there was evidence of inadequate blood supply to the distal end of the proximal esophagus in only one animal in our series, it is difficult to explain the failure of healing of the anastomosis on the basis of arterial insufficiency. The presence of wide anastomotic scars, as in Figure 6, suggests that tension may be the more important factor in the majority of instances, even though this might not be apparent at the time of operation. However, it may be said that the great elasticity of the thoracic esophagus explains the lack of tension in most cases after resection of such lengths as are reported in this series.

The greatest length of the esophagus that could be resected and followed by restoration of continuity by means of end-to-end anastomosis in the dog without prohibitive mortality was not ascertained.

Observations on the possible effects of complete disruption of the thoracic nerve supply on the function of the esophagus are not justified on the basis of this study.

The clinical observations support the following beliefs:

In the first case, sufficient margins of grossly normal esophagus on either side of the tumor were not excised because of fear of too great tension on the anastomosis. Considering the narrow margins, recurrence was not unexpected.

In the second case, the presence of contiguous carcinoma of the trachea, with its perforation, may have been a factor in the failure of the anastomosis to heal. It suggests that perhaps the interposition of a pedicle flap of normal tissue would have increased the chance of success. It also suggests that the operation might have been performed with greater chance of success if it had been done because of distant metastasis rather than of invasion of immediately surrounding tissue.

SUMMARY

1 Resection of approximately 33 per cent of the lower half of the thoracic esophagus, with restoration of continuity by end-to-end anastomosis, was performed on 21 dogs without the use of adjuvant therapy.

2 The mortality in the dogs was approximately 33 per cent, regardless of the side of approach or of variations in technique

3 The cause of death in the majority of the seven animals that failed to survive was infection due to partial or complete disruption of the anastomosis. In only one animal was there evidence of lack of blood supply to the proximal and distal ends of the esophagus after complete separation and dislocation of the thoracic esophagus from its mediastinal bed

4 Among 14 animals surviving and sacrificed at intervals of from two weeks to eight months following operation, the esophagus was essentially normal in the majority. In only one was there a slight stricture at the site of the anastomotic scar

5 The application of the operation as a palliative procedure in two cases of inoperable carcinoma of the esophagus is described

6 In the first case, one of primary carcinoma of the lower thoracic esophagus, the operation was successful temporarily in that the ability to swallow was restored for a period of three months prior to recurrence

7 In the second case, one of secondary carcinoma of the upper thoracic esophagus, the operation was a failure due to partial disruption of the anastomosis and the development of an esophagotracheal fistula in the presence of contiguous carcinoma of the trachea

8 It is believed that the operation may have a place in the treatment of selected cases of inoperable carcinoma of the esophagus, as a method of palliation superior to others in use at present

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DISCUSSION —DR WILLIAM F. RIENHOFF, JR., Baltimore. I have enjoyed Doctor Bigger's presentation very much indeed, as I always do, and the subject of congenital atresia of the esophagus has been discussed by him in a most admirable way.

There are a few points I would like to make, which really only emphasize what Doctor Bigger stated, some of which he, because of lack of time, could not discuss as fully as he perhaps would have wished. In the first place, I feel that congenital atresia of the esophagus constitutes an emergency of really major proportions and that the operation to correct this condition should not be postponed any longer than absolutely necessary. We feel that preoperative gastrostomy is not indicated and actually may do harm in the great majority of these cases. Unquestionably, an end-to-end anastomosis between the superior and inferior portions of the esophagus with closure of the trachea or esophageal fistula, as described originally by Cameron Haight, is the operation of choice.

However, in those cases in which there is absence of gas in the stomach or intestines, it would seem to indicate that there is either agenesis of the thoracic esophagus or an

hiatus between the two patent ends which would probably be too great to bring the ends together in order to perform an end-to-end anastomosis. In such cases it is necessary to do a cervical esophagostomy in order to prevent saliva from spilling from the blind end pouch into the lung thus causing death from pneumonitis. In two cases in which there was complete agenesis of the thoracic esophagus, one patient 5 and the other 8 days of age, it was necessary to use the stomach by bringing the latter organ out of the abdominal cavity, following which it was brought up over the chest wall in the subcutaneous tissue and anastomosed to the cervical esophagus above the clavicle. After the stomach was brought up through the chest wall subcutaneously and cervical esophagostomy was done, the blind end of the superior pouch, also placed subcutaneously in the neck, was joined to the cardiac end of the stomach just at the level of the clavicle. The children were explored through the abdomen via a left subcostal incision. I was very much surprised at the ease with which the stomach could be completely mobilized by cutting the left gastric and gastroepiploic vessels, together with the vasa breva. In a child so young the stomach is much larger in proportion to the length of the chest than in any other age subsequently, and the gastric vessels are so small that there is no difficulty whatsoever in the control of hemorrhage. Each operation consumed an hour and, until one has performed this complete mobilization of the stomach, bringing it out through the left costal incision, one will not be impressed properly with the facility and ease with which it can be done. In both these cases it would have been impossible to establish the continuity of the gastro-intestinal tract by any other method. I think any intrathoracic operation in a child that age would not have been successful. It was quite remarkable—and I discussed this problem with Doctor Blalock many months ago—that these very young children, only a few days old, do not seem to be subject to shock, at least in these two babies there was not the slightest evidence of shock at any time during or after the operation. These cases were reported in the *Johns Hopkins Bulletin* (Vol 82, No 4, April, 1948).

With reference to Doctor Parker's paper, I enjoyed this very much indeed. I have had three cases, one a lye stricture and two early operable carcinomas of the esophagus in which it was possible to resect the lower third of the esophagus by mobilizing the stomach very slightly, cutting the vagi in order to obtain more length and freeing the upper portion of the esophagus, after which an end-to-end anastomosis of the esophagus was performed. All three survived the operation well.

I might add that in the event that the esophagus can be so resected, mobilized and sutured, the length of time of operation is very much reduced and, which means much more to me, the cardiac sphincter mechanism is maintained so that there is no regurgitation of gastric contents into the lower end of the esophagus with the possibility of producing a peptic ulcer in the latter organ, or painful esophagitis. Undoubtedly, cutting the vagus nerves permits much more complete mobilization of the esophagus than has been generally recognized, and by enlarging slightly the normal esophageal hiatus, thus bringing the stomach up into the mediastinum for a short distance, it enabled me to easily approximate the cut ends of the esophagus in those instances in which at least four inches was resected. Of course, the stomach can be further freed by dividing the left gastric vessels, if need be.

DR R A DANIEL, Nashville, Tenn. Doctor Bigger has stressed the desirability of attempting to determine before operation the approximate length of the two segments, and this is extremely desirable, because in a fairly large proportion of these patients there is a wide gap between the upper blind pouch and the lower segment which is frequently very delicate in its structure. I would like to point out that the lower segment is fixed—that is, in the common 3-B type—by its attachment to the trachea, whereas the upper segment is not fixed, and with straining or attempts at swallowing there is marked retraction upward of the upper segment. Therefore, if iodized oil is placed in the upper segment and an x-ray film is made, one may get a false impression of the exact length of the upper segment. I think it is desirable to examine these children under the fluoroscope with a catheter in

the upper segment I think the idea of resecting a long segment of rib is a very good one I have removed short segments of three, four or five ribs, and have had trouble with perforation of the pleura by the ends of these segments An open pneumothorax is poorly tolerated and I am sure you all know that positive pressure anesthesia during the early part of the operative procedure, before the fistula can be closed, is an undesirable thing in a child whose stomach is blown up like a balloon by means of positive pressure anesthesia

With regard to Doctor Parker's paper, it seems to me that this work is important in the treatment of short benign strictures of the esophagus In carcinoma of the lower end of the esophagus we have carried out radical resection of the esophagus and mobilization of the stomach and esophagogastric anastomosis, in patients with widespread metastases, knowing the patients would ultimately die of carcinoma I think the possible advantage of such a procedure, even though it is a larger operation and more lengthy, is that in our experience these patients have not suffered from dysphagia subsequent to operation

DR I A BIGGER, Richmond, Virginia (closing) I wish to thank Doctor Rienhoff and Doctor Daniel for their discussions Doctor Daniel stated that positive pressure anesthesia during the preliminary stages of operation and up to the time the fistula is closed, will cause marked distention of the stomach and intestines This we think is one of the decided advantages of preliminary gastrostomy, because if the gastrostomy tube is left open one can institute pressure anesthesia at the beginning of the operation, and the air which passes down the distal esophageal segment escapes through the gastrostomy tube and does not produce gastric and intestinal distention

I think Doctor Rienhoff's idea is an excellent one This slide shows a child in whom we did a secondary procedure very similar to that described by Doctor Rienhoff We had gone in extrapleurally on the right side, hoping to be able to do an anastomosis, but end-to-end suture was not possible, so we closed the fistula and implanted the proximal segment of the esophagus in the right side of the neck A preliminary gastrostomy had been done Nine months later we excised the gastrostomy opening in the abdominal wall, closed the opening in the stomach, and then transplanted the stomach under the skin of the anterior chest wall as recommended by Rienhoff The esophagogastrostomy was done on the right side I do not believe it makes any difference on which side this operation is performed One other thing which we did may be of some advantage We excised the xiphoid, incised the diaphragm for 3 or 4 centimeters, and implanted the distal portion of the stomach in the area between the costal arches and sutured the margins of the diaphragm to it This maneuver provides a good groove for the stomach and may make it possible to make an anastomosis under somewhat less tension

This child had a fistula at the site of anastomosis which is not yet healed and apparently will require closure

DR. EDWARD F PARKER, Charleston, S C (closing) I would like to thank Doctor Rienhoff and Doctor Daniel for their discussions We did not mean to imply that we would consider using local resection with end-to-end anastomosis as a curative procedure Obviously the resection is too limited and it is intended to be only a resection of a primary tumor We have to agree with Doctor Daniel, in our experience thus far, that it may be better to go ahead and do a procedure of greater magnitude However, I would like to recall that whereas there was local recurrence in the first case because of inadequate resection of the segment, in the second case there was no evidence of persistence of carcinoma in the proximal or distal ends of the esophagus, on microscopic examination at autopsy

THE SURGICAL TREATMENT OF PULSION DIVERTICULA OF THE THORACIC ESOPHAGUS*

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PULSION DIVERTICULA of the esophagus are of unusual interest because of their indeterminate cause and infrequent occurrence, their fairly constant location in the lower third of the esophagus, the progressive character of their development and clinical symptoms, often simulating those of esophageal hiatal hernia, their frequent association with other conditions involving the lower part of the esophagus, such as spasm and esophageal hiatal hernia, and their treatment. Conservative treatment such as dietary measures and dilatation of the esophagus may be used when the diverticulum is small and causes minimal symptoms or is associated with spasm of the esophagus, but surgical intervention will be required if it progresses in size and causes retention of food or obstruction of the esophagus.

This paper is a report on a series of eight patients whom I have treated surgically. Seven were treated by transpleural excision of the diverticula and repair of the opening in the wall of the esophagus and one by invagination of the diverticulum and plication of the wall of the esophagus.

Diverticula may occur in any part of the esophagus. They are of two general types: pulsion diverticula and traction diverticula. This classification into two types was made by Rokitsansky¹ in 1840 and was based on their cause. A third type was described by Oekonomides² in 1882; he classified this type as a traction-pulsion diverticulum, which is a combination of the above-mentioned two types.

Traction diverticula are due to the cicatricial contraction caused by an inflammatory process which involves the outer wall of the esophagus. They are usually caused by inflammatory disease of the lymph nodes at the bifurcation of the trachea and the hilus of the lung, which become adherent to the wall of the esophagus. They are true diverticula, as their walls consist of all layers of the wall of the esophagus, and they are usually located in its middle third. They rarely produce clinical symptoms, and surgical treatment is not indicated unless complications arise such as perforation into the lung.

Pulsion diverticula are caused by pressure within the esophagus and are not true diverticula but essentially herniations of the mucous membrane through the muscle layers of the esophagus. One theory of origin is that they are due to a congenital defect in the muscle wall of the esophagus. Although they may be of congenital origin, they rarely occur or produce symptoms until middle life. Mondière³ in 1833 discussed the pathogenesis of esophageal

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diverticulum and related three possible theories of origin, which were "First, a hernia of the mucosa of the esophagus through a separation of the muscle fibers, second, the prolonged sojourn of heavy and small foreign bodies, third, any obstacle whatever to deglutition" Pulsion diverticula are most frequently located at the pharyngo-esophageal junction and extend through the muscle wall of the hypopharynx In this location they are commonly termed "pharyngo-esophageal diverticula" The next most common site of occurrence is in the lower third of the esophagus, where they are often called "supradiaphragmatic or epiphrenic esophageal diverticula", this latter term was introduced by Rosenthal⁴ in 1902 Reeves⁵ in 1855 introduced the term "esophagocele" for this pulsion type of esophageal diverticulum

In my experience the relative infrequency of pulsion diverticula of the esophagus as compared with pharyngo-esophageal diverticula is exemplified by the fact that I have treated surgically 216 patients with pharyngo-esophageal diverticula during the same period that I have treated eight patients with pulsion diverticula

Pulsion diverticula of the esophagus usually occur through the right posterior wall of the esophagus, from 3 to 4 inches (7.5 to 10 cm) from the cardia, and extend into the right thoracic cavity, although they may occasionally occur at a higher level in the esophagus and may occasionally extend into the left thoracic cavity In the eight patients in this series, the opening of the diverticula was in the middle third of the left wall of the esophagus and extended into the left thoracic cavity in one case, it was in the left anterior wall of the lower third of the esophagus and extended into the left thoracic cavity in one case, and in the remaining six cases the openings of the diverticula were in the right posterolateral wall of the lower third of the esophagus and the diverticula extended into the right thoracic cavity The frequency of the occurrence of these diverticula in the latter location suggests an embryonic origin due to a congenital defect in the wall of the esophagus at this location, although the fact that the average age of these patients was 52 years tends to refute this theory of origin

The youngest patient in this group was 42 years of age and the oldest 62 years Seven patients were men and one was a woman

SYMPTOMS

The first accurate description of the clinical symptoms and anatomic findings in a case of diverticulum of the lower part of the esophagus was made by Deguise⁶ in 1804 The following observation of the patient was quoted from his thesis "We were consulted in the case of M P ———, who, for more than 15 years, experienced, after having eaten, a type of rumination which returned to the mouth a part of the food which he had taken, at last he was attacked by pains, very great difficulty in swallowing, and died in the greatest emaciation At the opening of the corpse, on the lateral part of the esophagus a membranous sac was found which communicated with the lumen of the esophagus, in which foods were introduced, and which, by its form, its

direction, its distention, compressed the orifice of the stomach, and hindered the free entrance of food "

The symptoms of pulsion diverticulum of the esophagus progress with the increase in the size of the diverticulum and are often complicated by an associated spasm of the lower part of the esophagus. In four of the eight cases of this series, there was an associated spasm of the lower part of the esophagus. The early symptoms are usually those of food sticking in the throat, often associated with spasmodic, low substernal pain. As the diverticulum increases in size, it causes progressive dysphagia, choking attacks, regurgitation or vomiting of food soon after its ingestion or, at times, of food which was taken the day before and has been retained in the diverticulum. The sacculation may become of sufficient size to cause pressure on and distortion of the lumen of the lower part of the esophagus, resulting in obstruction and marked loss of weight. The retained food and secretions may cause pronounced inflammation and ulceration in the wall of the diverticulum, which may be followed by perforation into the lung or mediastinum.

The symptoms associated with these diverticula often simulate those produced by the esophageal hiatal type of diaphragmatic hernia or those produced by a diverticulum of the cardiac end of the stomach. The differentiation can rarely be definitely made clinically but it can usually be made by the roentgenologic and esophagoscopic examination of the esophagus and cardiac end of the stomach. Reitzenstein⁷ in 1898 is credited with the first roentgenographic confirmation of the diagnosis of esophageal diverticulum.

Roentgenographic and esophagoscopic examinations are very important, not only in establishing the clinical diagnosis of the presence of a diverticulum but also in determining the presence of other associated conditions such as spasm of the lower part of the esophagus, an organic obstruction of the lower part of the esophagus that results from the presence of a tumor or stricture, or an esophageal hiatal hernia which may require treatment. In six of the eight cases of this series there was an associated small esophageal hiatal hernia. Only one of these six hiatal hernias was repaired surgically.

In one case of this series of esophageal diverticula, the lesion was reported both on roentgenoscopic and esophagoscopic examination as an esophageal hiatal hernia. This was due to the large size of the opening as well as to the large size of the diverticulum, which was less than 3 inches (7.5 cm.) from the cardia, the lumen of the esophagus below the opening was very small. There was an associated small hiatal hernia which was repaired first and the diverticulum was operated upon later. In one other case at the first roentgenologic examination only a hiatal hernia was reported, but at a second examination the shadow originally interpreted as an esophageal hiatal hernia was reported as a diverticulum of the esophagus with an associated small esophageal hiatal hernia.

The roentgenologic and esophagoscopic examinations are not only important in the establishment of the clinical diagnosis but are also of equal importance in the surgical consideration of these diverticula. The more important of these considerations are determination of the size and site of origin of the

diverticulum from the lumen of the esophagus and the side of the thorax into which the diverticulum extends from the posterior mediastinum. These examinations are important in determining the most accessible point of approach through the thoracic wall to expose the diverticulum, in determining whether there is any retention of food or foreign body in the sac, which, if present, should be thoroughly removed before operation, and also in determining whether there is any communication between the diverticulum and the lungs or mediastinum as a result of perforation which would require special preoperative preparation and treatment at the time of removal of the diverticulum. In none of the eight cases of pulsion diverticulum herein reported was there any perforation into the lung. In one case in which the diverticulum was in the middle third of the esophagus, the walls of the diverticulum were greatly inflamed and calcified and the diverticulum was adherent to the median surface of the left lung but had not perforated into the lung. However, I operated upon a patient on July 11, 1928, who had a traction type of diverticulum of the middle third of the esophagus due to inflamed mediastinal lymph nodes, this diverticulum had perforated into the posterior median surface of the lower lobe of the right lung and right main bronchus. A right transpleural one-stage diverticulectomy and closure of the bronchial fistula were performed. This patient is not included in this series because the diverticulum was of the traction type.

PREOPERATIVE TREATMENT

The preoperative preparation is important in those patients who are selected for surgical treatment. As stated above, if there is any retention of food or foreign material in the sacculation, it should be thoroughly removed before operation, in some instances this retained material may become inspissated and incrustated onto the walls of the diverticulum so that removal of it may require repeated endoscopic aspirations, in some instances the patient can greatly assist in freeing or can completely free the diverticulum of retained material by swallowing liquids. This procedure they often carry out after meals to relieve their distress.

The diet should be of a liquid or nonresidue type after the sacculation has been freed of residue.

All patients have at least one dilatation of the esophagus below the diverticulum before operation. Patients who have an associated spasm of the lower part of the esophagus may require more dilatations before operation than do those without spasm. All patients are given penicillin as an aerosol and by intramuscular injection for from 24 to 48 hours before operation, and a Rehfuess tube is passed through the esophagus into the stomach at the time of operation so as to prevent vomiting and keep the stomach empty during and after operation. The tube is also an aid in locating the lumen of the esophagus at operation.

OPERATION

The more important technical considerations of the surgical treatment of a large pulsion diverticulum with herniation of the mucous membrane through

an opening in the muscle wall of the esophagus are the selection of the most accessible site of transpleural approach to the diverticulum, the separation of only sufficient mediastinal pleura from the esophagus to permit adequate exposure of the diverticulum with as little separation of the esophagus from

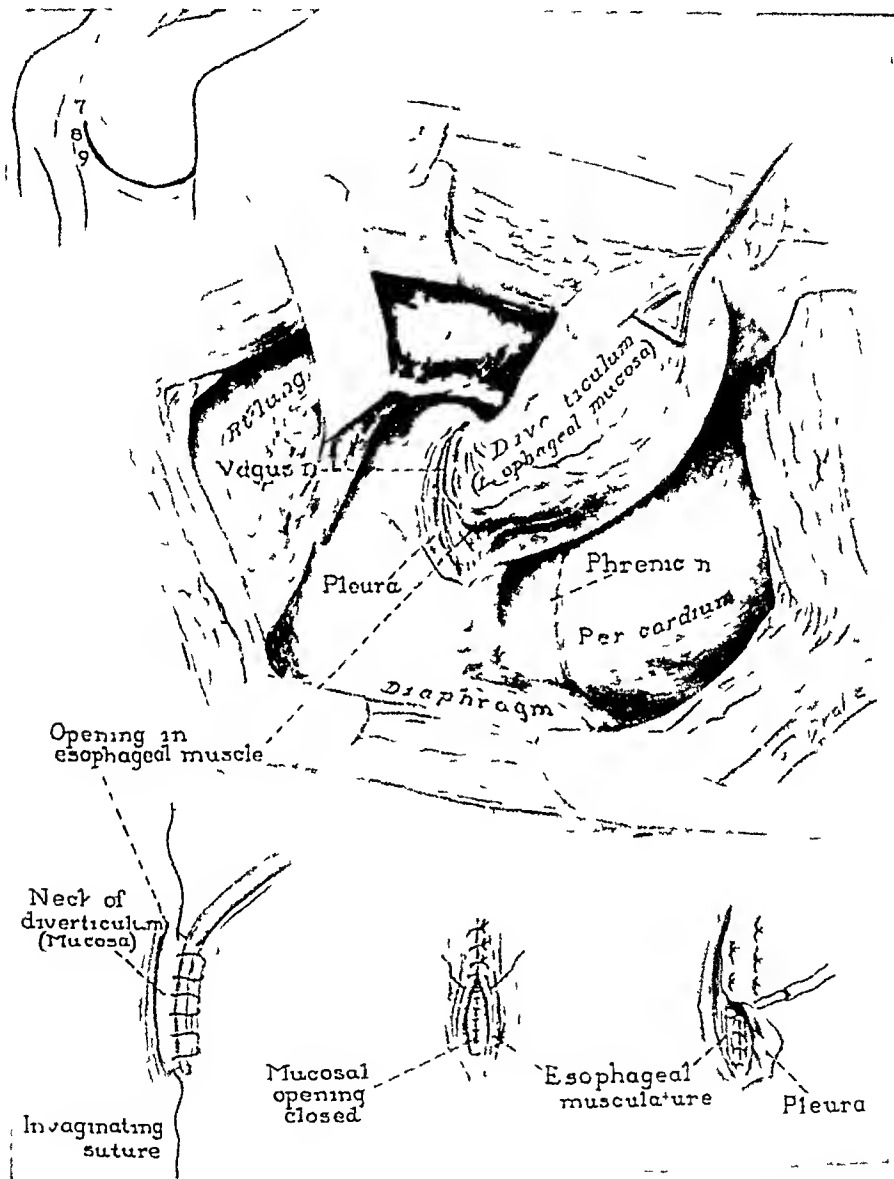


FIG 1—Pulsion type of diverticulum of the lower part of the esophagus 3 inches (7.6 cm) above the diaphragm. Right posterolateral transpleural approach, and technic of one-stage diverticulectomy and reconstruction of the wall of the esophagus.

its mediastinal bed as possible, complete excision of the sacculization, and the repair and reconstruction of the opening in the wall of the esophagus. In the cases in which the diverticulum is excised, it is essential that the herniated mucous membrane be completely separated from the muscle wall at its opening, and great care should be taken not to penetrate the mucous membrane

during the dissection. After the neck of the sacculation has been completely separated, a soft right-angle clamp is placed at least 1.5 cm from the true opening and the diverticulum is excised at this point so as to leave sufficient mucous membrane for inversion into the lumen of the esophagus without leaving any redundancy or causing any constriction of the lumen of the esophagus. A Connell suture of continuous chromic catgut is used to invaginate the neck of the sac into the lumen of the esophagus. The opening in the muscle wall of the esophagus is then closed with two rows of interrupted silk sutures, care being taken not to narrow the normal lumen of the esophagus (Fig. 1). In those cases in which there is a dilatation of the muscle wall of the esophagus associated with a moderate-sized diverticulum, the sacculation may be excised, the opening closed and the wall of the esophagus plicated to normal size. When the diverticulum is small and associated with dilatation of the muscle wall of the esophagus, the sacculation may be invaginated with plication of the esophageal wall. After the diverticulum has been excised and the wall of the esophagus has been reconstructed, the median fold of the mediastinal pleura is sutured over the closure and the posterior fold is left open for drainage of the posterior mediastinum. Three hundred thousand units of penicillin are placed in the pleural cavity. The lung is fully inflated by positive pressure, and the incision in the thoracic wall is closed with intercostal closed drainage under water seal or gentle suction for from 48 to 72 hours.

Brief reports of the eight cases of pulsion diverticula of the lower esophagus of this series follow.

REPORT OF CASES

Case 1—A man age 42 years was admitted to the clinic on October 8, 1940. His chief complaint was dysphagia of 10 years' duration. He stated that he had had a tonsillectomy 10 years prior to admission, which was complicated by an aspiration pulmonary abscess on the right side. Since that time he had had recurrent attacks of spasmodic pain in the lower part of the esophagus associated with sticking of food in his esophagus, which was more severe after nervous strain. He had been given belladonna with temporary relief. Three weeks prior to his admission, after a severe nervous strain, he began to have marked dysphagia and retrosternal and retroxiphoid pain that extended to the posterior part of the throat, and he had difficulty in swallowing food or liquids. There was no vomiting or regurgitation of food. He had lost 10 pounds (4.5 Kg). A diagnosis of diaphragmatic hernia had been made on roentgenologic examination.

Roentgenologic study of the stomach and duodenum at the clinic gave negative results. The roentgenologic study of the esophagus revealed an esophageal diverticulum, 5 cm in diameter, in the right posterior wall of the lower third of the esophagus. Esophagoscopy disclosed a large pulsion diverticulum with a large opening in the right posterior wall of the esophagus, 1½ inches (3.8 cm) above the cardia. There was no ulceration of the mucous membrane of the diverticulum, which contained a large amount of barium and mucoid secretion. There was no obstruction of the esophagus below the opening of the diverticulum. The patient's symptoms improved after esophagoscopy and dilatation of the lower part of the esophagus. He was advised to have surgical intervention for the diverticulum but refused. He was advised to return in three months for observation but he did not return until one year and four months after his dismissal. The roentgenograms at the second visit revealed marked increase in the size of the diverticulum to 8 cm in diameter, and the esophagoscopy examination disclosed consid-

erable increase in the size of the opening of the diverticulum and inflammation of the mucous membrane of the diverticulum and the lower part of the esophagus. Surgical intervention was again advised, and on March 4, 1942, a right transpleural diverticulectomy was carried out (Fig 2a, b and c).

After the operation right pleural effusion developed, this required several pleurocenteses and was followed by open operation because of empyema on the right side. Esophagoscopic examination revealed a small opening from the right lateral wall into the mediastinum. The patient was unable to tolerate a nasal tube, so a gastrostomy was performed for feeding. His condition improved after the gastrostomy, and at the time of his dismissal the empyema cavity was granulating well and there was no leakage from the esophagus. He returned to the clinic on several occasions and at the time of a visit seven months after operation, the roentgenogram of the esophagus revealed some dilatation of the lower part of the esophagus on the right, probably at the site of the former diverticulum. He was feeling well.

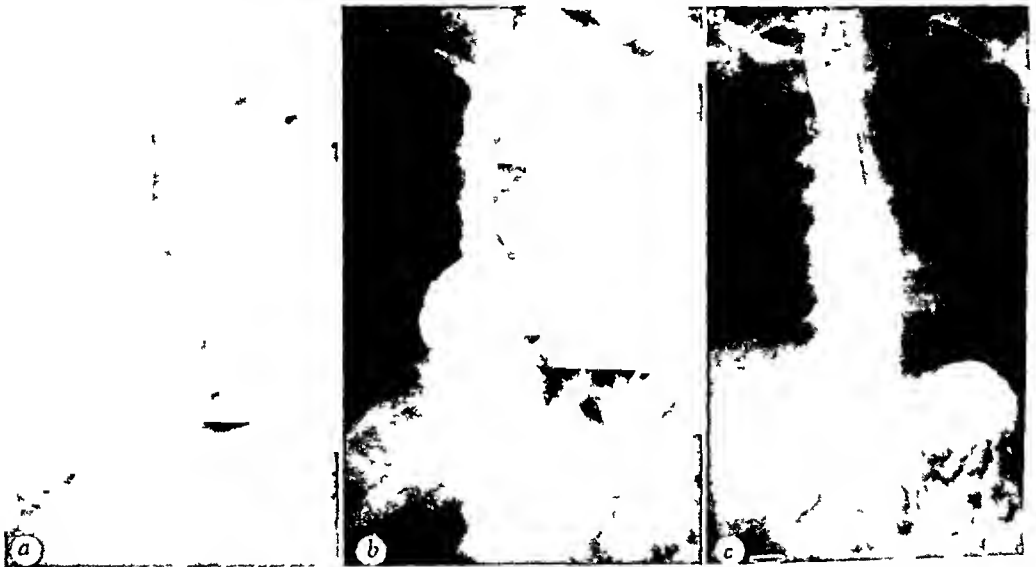


FIG 2—Pulsion diverticulum of the lower third of the esophagus. Right transpleural one-stage diverticulectomy with reconstruction of esophagus (a and b). Progressive increase in size of diverticulum in a period of one and one-third years (c). After transpleural diverticulectomy and reconstruction of the esophagus. Recovery complicated by empyema. Some dilatation at the site of operation, with narrowing of the esophagus below, due to spasm. Complete relief of symptoms.

Case 2—A woman age 57 years was admitted to the clinic on October 12, 1943. Her chief complaints were dysphagia and substernal distress of seven months' duration, and asthma since 1923. Seven months prior to her admission, the patient had begun having difficulty in swallowing food. She had a sensation that food was stopping behind the sternum. Three months after the onset, solid food was difficult to swallow and caused distress under the sternum, with regurgitation of food almost immediately. Three weeks later, roentgenographic examination revealed a diverticulum of the esophagus just proximal to the cardia. The patient had lost 30 pounds (13.6 Kg) during the past four or five months. She also gave a history of having had asthma since the fall of 1923. She had been relatively free from symptoms of asthma during the past three years except when she had a cold.

The roentgenographic examination of the esophagus and stomach revealed an esophageal hiatal hernia and, about 4 inches (10 cm) above the stomach, a diverticulum. A second roentgenogram of the esophagus disclosed a large diverticulum of the lower third of the esophagus and a small esophageal hiatal hernia with about 2 inches (5 cm)

of the stomach above the diaphragm. Esophagoscopy examination revealed a large diverticulum in the left wall of the lower third of the esophagus. The contents of the diverticulum were aspirated. Reduction in weight was advised. The patient returned to the clinic after two months, stating that the condition had become worse and that she was now unable to take liquids. A diagnosis was made of a large, infected pulsion diverticulum in the lower third of the esophagus and of a small esophageal hiatal hernia. Surgical intervention was advised for the esophageal diverticulum, and on October 23, 1943, a left transpleural diverticulectomy was carried out.

The immediate convalescence was essentially uneventful except for moderate difficulty in swallowing solids. The patient was dismissed from the hospital on the fortieth post-operative day but, because of an influenzal pulmonary infection, was readmitted. Because of the pulmonary infection, an open operation with resection of the ninth rib was required,

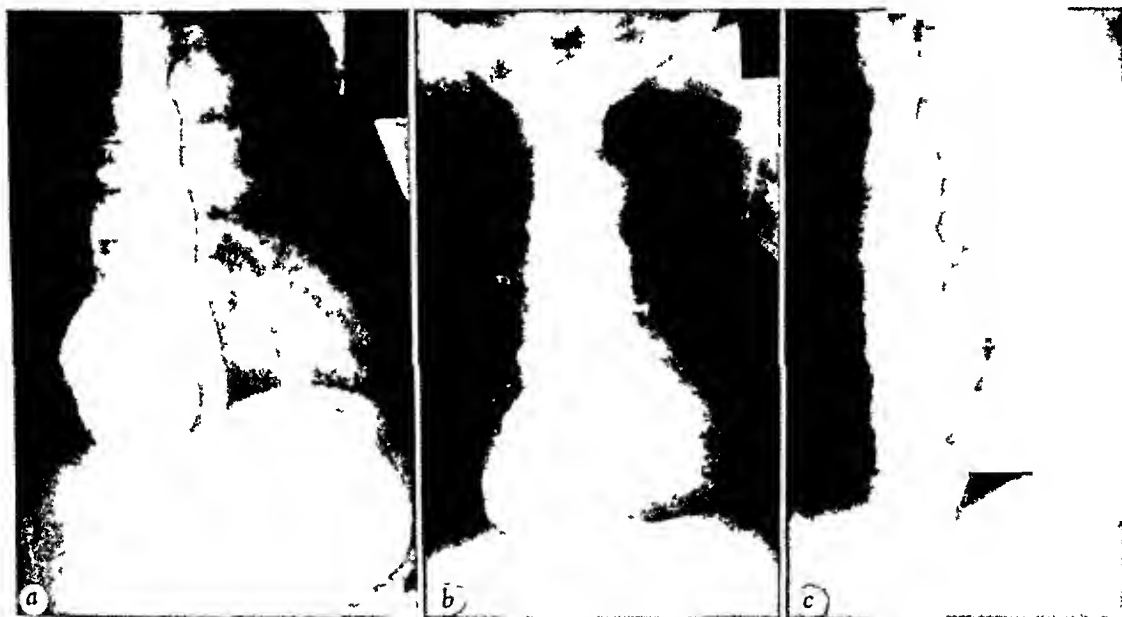


FIG 3—Large pulsion diverticulum with retention in the lower fourth of the esophagus. Right transpleural one-stage diverticulectomy with reconstruction of the esophagus. (a) On admission, showing esophageal diverticulum extending into right thoracic cavity and to the diaphragm. (b) Twenty-four hours later, showing retention of barium in the diverticulum. (c) On dismissal, 24 days after diverticulectomy. Esophageal deformity at the site of operation. Lumen of esophagus normal. Relief of symptoms.

after which she gradually recovered. At the time of her dismissal, two and one-half months after the diverticulectomy, the roentgenogram revealed a sacculatation at the point of operation. The wound was healed, except for a granulating area in the posterior angle. She returned for observation three years after operation. She still had some dysphagia but her symptoms were markedly relieved.

Case 3—A man age 59 years consulted the clinic on May 30, 1945, complaining of stomach trouble of 10 years' duration. He stated that for 10 years prior to his admission, he had had progressive difficulty associated with ingestion of food. He had two types of difficulty: (1) a progressive dysphagia, he stated that food or liquids did not seem to enter his stomach but that they were regurgitated into his throat causing a marked choking, and (2) a feeling of fullness high in his epigastrium after meals, with vomiting and regurgitation of food. He often regurgitated food which had been taken two days previously. He had this difficulty with both liquids and solids, particularly with cold drinks. There was also a burning, gnawing sensation in the epigastrium after meals, which would be particularly relieved by soda. He had lost 15 pounds (6.8 Kg).

The roentgenogram of his esophagus revealed a large diverticulum, about 10 cm in diameter, arising from the distal third of the esophagus. An esophagoscopy examination was carried out, with partial removal of the contents of the diverticulum. It was impossible to remove all the food, barium and debris from the diverticulum by endoscopic aspiration, and the patient assisted in freeing the diverticulum of retained material by swallowing liquids. A diagnosis of a pulsion diverticulum of the lower fourth of the esophagus was made, and on June 13, 1945, a right transpleural diverticulectomy was performed (Fig 3a, b and c). The patient made an excellent recovery from the operation and was dismissed four weeks after the operation. The roentgenogram of the esophagus revealed the site of the operation to be in good condition with a good lumen of the esophagus.

Case 4—A man age 43 years consulted the clinic on February 3, 1945. His chief complaint was stomach trouble of four years' duration and dysphagia of six months' duration. He stated that in 1941 he had consulted his physician because of stomach trouble with pain and some dysphagia. He had also had diarrhea and the condition, he said, was diagnosed as spastic colitis. In June, 1944, he began having difficulty in swallowing food. The food seemed to lodge in his esophagus. He would become nauseated and would vomit the food to get relief. This condition has become gradually worse until the time of his admission, when he could swallow only liquids. He had lost 50 pounds (22.7 Kg.).

The roentgenogram of the stomach revealed an esophageal hiatal hernia with a portion of the cardinal end of the stomach above the diaphragm. The roentgenogram of the thorax disclosed a rounded mass of increased density behind the right portion of the heart. Esophagoscopy examination revealed nothing abnormal. A diagnosis was made of a small hiatal diaphragmatic hernia due to an incompetent esophageal hiatus, and on February 10, 1945, the hernia was repaired. It was found that the sacculization seen on roentgenoscopic examination was not due to the hernia but was due to a pulsion diverticulum of the lower part of the esophagus. The patient made a good recovery from the operation and was dismissed three weeks after operation. He was advised to return later for removal of the diverticulum. He returned on June 14, 1945, and esophagoscopy examination revealed a large diverticulum in the lower end of the esophagus, containing about 500 cc of food, which was removed. He complained that he had had further loss of weight and increasing dysphagia since his previous dismissal. A diagnosis of pulsion diverticulum of the lower third of the esophagus was made, and on June 14, 1945, a right transpleural diverticulectomy was carried out.

The postoperative course was satisfactory, and the patient was dismissed from the hospital on the sixteenth postoperative day. A letter received a year after the operation stated that his condition was much improved. A roentgenogram taken by a physician in his home community revealed the esophagus to be normal except for a slight irregularity at the lower end.

Case 5—A man aged 62 years consulted the clinic on April 9, 1946, because of a sense of fullness and distress behind the lower end of the sternum of six years' duration. He stated that this feeling of fullness and distress became worse one or two hours after meals, at which time he experienced considerable eructation of sour food. During the six or eight months just prior to his admission he had to sleep on two or more pillows. If he lay flat, he would vomit a large amount of food. He had no nausea and there was no weight loss. He had consulted a physician in his home community, who had diagnosed the condition as a pulsion diverticulum of the lower part of the esophagus, and repeated roentgenograms had revealed increase in the size of the diverticulum.

A roentgenogram of the stomach and the esophagus revealed a large diverticulum in the right lateral aspect of the terminal end of the esophagus and a small hiatal diaphragmatic hernia. Esophagoscopy examination revealed a fair amount of gastric secretion in the esophagus and considerable spasm around the orifice of the diverticulum. The food content was aspirated from the diverticulum. A diagnosis was made of pulsion

diverticulum of the lower part of the esophagus, with constriction of the distal portion, and a small hiatal diaphragmatic hernia. Surgical intervention was advised for the pulsion diverticulum, and on April 18, 1946, a right transpleural diverticulectomy was performed. Convalescence was uneventful, and the patient was dismissed four weeks after the operation. The roentgenogram of the esophagus revealed considerable spasm of the lower part of the esophagus, which was otherwise normal. Also a small hiatal diaphragmatic hernia was present.

Case 6—A man age 55 years consulted the clinic on June 18, 1946. He complained of dysphagia of 10 years' duration. Because of his difficulty in swallowing he had consulted his physician, who he said, had made a diagnosis of nervousness. Two years prior



FIG 4—Pulsion diverticulum of the middle third of the esophagus. Spasm of the lower part of the esophagus. Small esophageal hiatal hernia. Left transpleural invagination of the diverticulum and plication of the wall of the esophagus (a). On admission. Diverticulum of the left middle third of the esophagus. Dilatation of the esophagus above the diverticulum and spasm of the esophagus below the diverticulum. Small esophageal hiatal hernia (b and c). Three weeks after operation. Some irregularity of the middle third of the esophagus at the site of operation. Small esophageal hiatal hernia. Left posterolateral incision healed. Relief of symptoms.

to his admission, the condition had become worse and roentgenograms revealed a diverticulum of the middle third of the esophagus and a hiatal diaphragmatic hernia. The patient had lost nine pounds (4.1 Kg) in two years. His only complaints were dysphagia and a sensation of food sticking in his thorax.

A roentgenogram of the esophagus revealed a diverticulum, with a very broad neck, in the esophagus at the level of the body of the seventh dorsal vertebra and a small esophageal hiatal diaphragmatic hernia. Esophagoscopy disclosed a large diverticulum of the anterior wall of the middle third of the esophagus and also a small hiatal hernia. A diagnosis of a pulsion diverticulum, with spasm, of the middle third of the esophagus, together with a small hiatal diaphragmatic hernia, was made, and on June 27, 1946, a left transpleural invagination of the diverticulum and plication of the esophageal wall were carried out. The patient made an uneventful recovery from the operation and was dismissed four weeks later (Fig 4a, b and c). The roentgenoscopic study of the esophagus revealed minimal irregularity of the middle third at the site of the former diverticulum and a small esophageal diaphragmatic hernia.

Case 7—A man age 48 years consulted the clinic on February 8, 1946, because of attacks of acute indigestion of two months' duration. He stated that two months prior to his admission he had had an attack of severe pain in the epigastrium and nausea. He consulted his physician, who took a roentgenogram of his stomach and found a diverticulum of the lower part of the esophagus. He had been placed on a diet and had lost 15 pounds (68 Kg). Other than a similar attack one year previously, he had had no symptoms.

A roentgenogram of the esophagus disclosed a large diverticulum arising from the lower part of the esophagus and a small esophageal hiatal hernia. Esophagoscopy examination revealed a great deal of material in the esophagus, and the large diverticulum in the lower part of the esophagus was filled with barium, which was aspirated. A small



Fig 5—Case 8. Pulsion diverticulum and spasm of the lower third of the esophagus. Right transpleural diverticulectomy. Small esophageal hiatal hernia. (a) On admission. Diverticulum of the lower third of esophagus with contraction and diffuse spasm of the distal part of the esophagus. Also esophageal hiatal hernia. (b) Three weeks after diverticulectomy. Spasm and contraction of the lower part of the esophagus. No deformity at the site of operation. Small esophageal hiatal hernia. (c) Pulsion diverticulum consisting of mucous membrane of the lower part of the esophagus. Some inflammatory reaction.

hiatal diaphragmatic hernia was also noted. A diagnosis was made of a pulsion diverticulum of the lower part of the esophagus and a small esophageal hiatal hernia. Surgical intervention was advised for the diverticulum. However, the patient refused surgical treatment at that time but returned in May, 1947, for further consideration because of continued trouble. He was again advised to have surgical intervention because of the esophageal diverticulum, and on May 5, 1947, a right transpleural diverticulectomy was carried out. His convalescence was complicated by pneumonia, and on the eighth day after operation pain developed in the right lower part of the thorax. This was followed by a second rise in temperature to 102° F, with increase in the pulse rate to 120 per minute. He was given penicillin but his condition did not improve and he died on the thirteenth postoperative day from pneumonia and a localized mediastinal abscess.

Case 8—A man age 47 years consulted the clinic on October 15, 1947, because of regurgitation. He stated that for two years he had been awakened frequently during

the night, at which time he would regurgitate a mouthful of bile-tasting fluid, usually he would reswallow the material. Occasionally, by force, he would vomit partly digested food although he never felt like vomiting. After vomiting, he would have a vague indigestion for several days. Frequently while eating at formal occasions, he would experience regurgitation of food just eaten.

A roentgenogram of the esophagus disclosed a diverticulum of the right wall of the lower part of the esophagus, with contraction of the distal part of the esophagus, and also a small hiatal diaphragmatic hernia. Esophagoscopy revealed no obstruction in the esophagus. A diagnosis was made of a pulsion diverticulum and spasm of the lower third of the esophagus and a small hiatal diaphragmatic hernia. Operation was advised, and on October 22, 1947, a right transpleural diverticulectomy was carried out. The patient made an excellent recovery from the operation and was dismissed three weeks after it (Fig 5a, b and c). He returned for observation seven months later. He had no symptoms. The roentgenogram of the esophagus disclosed moderate redundancy of the esophagus at the site of the removal of the diverticulum and diffuse spasm of the lower part of the esophagus, as well as a small hiatal diaphragmatic hernia. Esophagoscopy revealed a shallow pouch in the lateral wall of the esophagus just above the stomach. The esophagus was dilated to the size of a 50 F sound without evidence of obstruction.

A brief summary of the surgical treatment in the eight cases of this series follows. The approach was transpleural through a posterolateral incision in all eight cases. In six the approach was through the right lower wall of the thorax, in one through the left lower wall and in one through the left midwall.

A diverticulectomy with repair and reconstruction of the muscle wall of the esophagus was done in seven cases. In the remaining case an invagination of a small diverticulum with plication of the dilated walls of the esophagus was done.

In one of the eight cases a repair of an esophageal hiatal hernia was performed prior to the excision of the diverticulum.

One patient had a postoperative empyema, which was drained first by closed intercostal drainage and later by open operation with rib resection. This patient could not tolerate an indwelling Rehfuess tube through the esophagus, and a temporary gastrostomy was done for feeding during the first two weeks of his postoperative convalescence following the open operation for drainage of the empyema. He made a satisfactory recovery.

One patient died from pneumonia and a small localized posterior mediastinal abscess on the thirteenth postoperative day.

Seven of the eight patients operated on recovered from the operation and have been relieved of their symptoms due to the diverticulum, three of these patients have continued to have some attacks of esophageal spasm.

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ESOPHAGEAL RUPTURE COMPLICATING CRANIOTOMY — SYMPTOM COMPLEX AND PROPOSED SURGICAL TREATMENT*†

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EMORY UNIVERSITY, GA

RECENTLY three esophageal ruptures occurred following what might have been successful craniotomies, all within a period of six weeks of one another, these cases aroused our interest in this tragic complication. We feel, after a study of the clinical course of these three patients and the only other two cases recorded in detail in the medical literature (Cushing⁴), that the symptom complex of this craniotomy sequel is such that the condition can be recognized before death. Since the symptomatology of this mediastinal insult in many of its features is analogous to the symptomatology of cerebral complications following craniotomy, it is quite likely that damage to the alimentary tract occurs more frequently than is suspected. By calling attention to the condition, we hope that it may be recognized that the true incidence of its occurrence may be established, and, with the suggested plan of treatment outlined by our confreres in thoracic surgery, that some of the fatally complicated craniotomies may be salvaged. For neurosurgic consideration, the salient symptoms of the esophageal complication are detailed, and for the surgeon versed in the technical problems of the mediastinal territories, a plan of treatment is offered for evaluation.

The clinical and experimental observations of the past have established the relationship between cerebral disease and ulceration and perforation of the alimentary tract. The literature on this subject, dealing with problems experimental, anatomic and pathologic, is voluminous. For our purpose, only the esophageal damage secondary to cranial surgery is of immediate concern. Aside from Cushing's contribution, it is important to recognize the earliest recorded efforts which form the basis for our present-day concepts of the neurogenic origin of gastro-intestinal mucosal denudements. This is particularly pertinent in view of the present extensive interest in the subject and in view of surgical efforts, both experimental and clinical, in the evaluation of the effects of vagotomy in the treatment of peptic ulcer.

In 1841, Von Rokitsky,¹ in his handbook on pathologic anatomy, described ulcerative lesions of the alimentary tract secondary to morbid conditions of the vagus nerve. He described esophageal and gastric perforations during life with effusions into the pleural and peritoneal cavities in cases of hypothalamic tumors. To Von Rokitsky credit is due for the adage, "ulcer in the alimentary tract—disease in the brain." In 1845 Schiff² carried out the earliest experimental procedures to confirm the relationship between cerebral

* From the Department of Surgery, Emory University School of Medicine, Emory University, Georgia.

† Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 7, 1948.

lesions and intestinal-tract damage. He effected unilateral lesions in the optic thalamus and adjacent cerebral peduncles in dogs and rabbits. Within a few days, he demonstrated a softening in the walls of the stomachs of these experimental animals and often an actual gastric perforation. Twenty-two years later, Schiff³ compiled all his work on the physiology of digestion and pointed out that there were vasoconstrictor and vasodilator nerve fibers to the stomach, that the former passed by way of the celiac plexus, and that flushing effects of the gastric mucosa were produced by stimulating the fibers of the



FIG 1—Autopsy specimen of Case 1, (A) denoting the tumor location in this patient, (B) the location of the adamantinoma in Case 2, and (C) the site of the sphenoid ridge growth in Case 3

vagus nerve. In 1931, Cushing¹ completely reviewed all the literature pertaining to the subject of cerebral lesions as related to gastro-intestinal disease and discussed in detail nine cases of his own that developed alimentary lesions following craniotomy. He clarified many questionable points on this subject of the relationship of cerebral disease to gastro-intestinal lesions and postulated from the study of his cases and additional experimental observations, "the presence in the diencephalon of a parasympathetic center." Important for the moment is his inference of the infrequency of gastro-intestinal complications

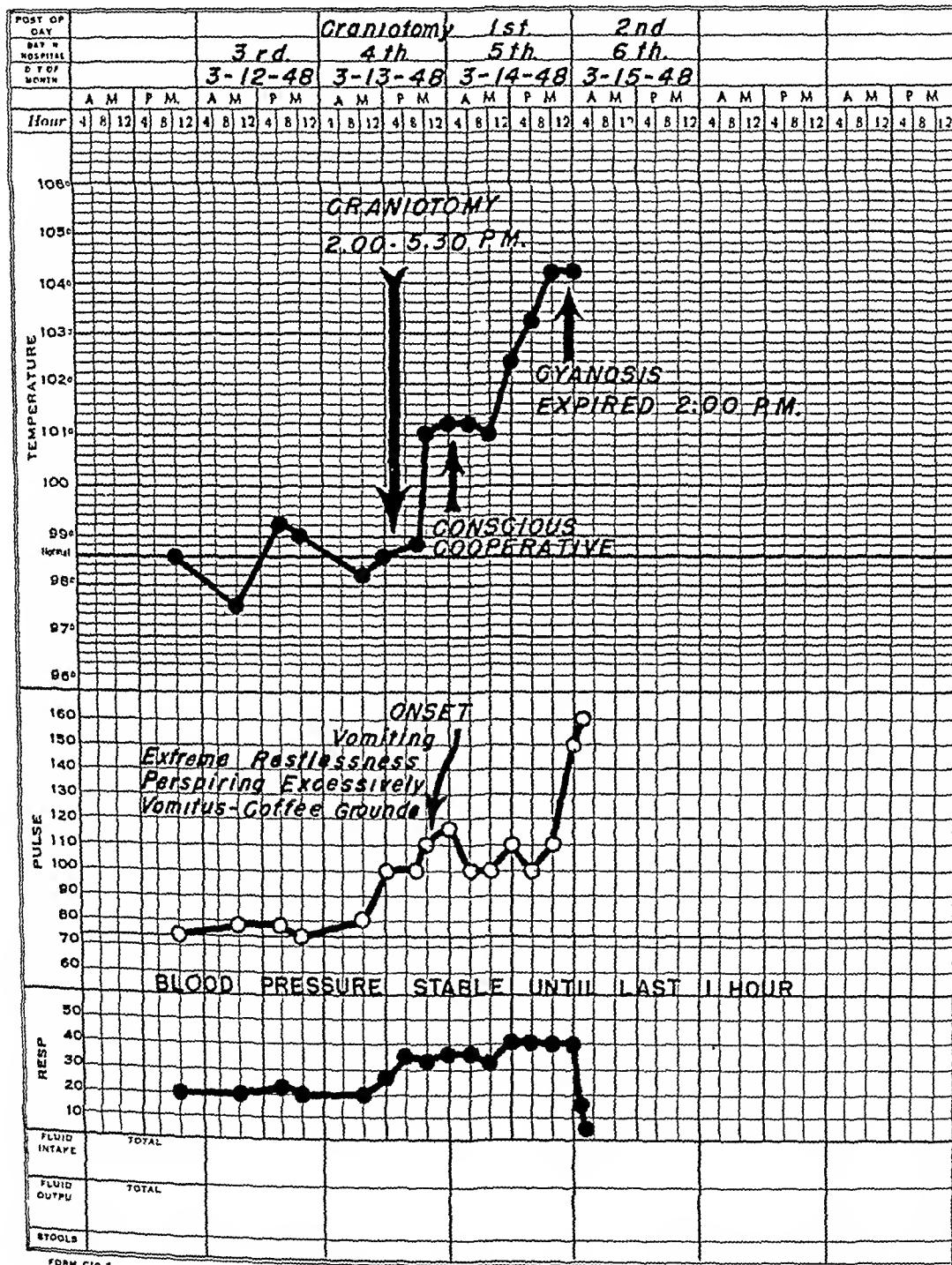
ESOPHAGEAL RUPTURE COMPLICATING CRANIOTOMY

EMORY UNIVERSITY HOSPITAL

GRAPHIC CHART

RECORD NO 10717U

NAME MRS. A. D. AGE 35 YRS. SERVICE OR DOCTOR Neuro-surg. 48 240



FORM C10 3

GRAPHIC CHART

FIG 2 (Case 1) See text

following craniotomy, for in 1931 Cushing's series of verified brain tumors was past the one thousand total. Further suggesting the rarity of esophageal ruptures is the fact that of the total of Cushing's 12 cases exhibiting gastro-intestinal pathology, he had only 2 in which the esophagus was torn.

Cushing's interest in the subject of ulcerations of the intestinal tract derived from "the disturbing experience of having lost three patients from acute perforations of the upper alimentary canal." That each of the brain tumors in his three cases "happened to be situated in the cerebellum could not," he said, "be other than of some significance." Our three tumors were all located above the tentorium and the anatomic site of our surgical activities involved the frontal and the anterior part of the middle cerebral fossae (Fig 1). It would appear that the importance attached by Cushing to the tumor locations as a factor in the production of gastro-intestinal lesions is not too significant. In our experiences, the region of the tuber cinereum was implicated in each case. This would support Cushing's idea of "the presence in the diencephalon of a parasympathetic center." The fiber tracts originating in the tuberal center "apparently pass backward to relay with the cranial-anatomic stations of the midbrain and medulla, of which the vagal nucleus is by far the most important, etc." From this still ill-defined anatomic suggestion, it is not yet possible to ascribe an isolated tumor location with a possible postoperative esophageal rupture. It is recommended that one might be more conscious of this craniotomy complication in any cranial surgical venture. Particularly, this possibility should be kept in mind when the surgery is performed in the hypothalamic or the medullary areas. There are clinical and experimental suggestions that gastro-intestinal function is cortically represented in the subfrontal convolutions. In our first experience (Fig 1), owing to the involvement of the most anterior pole and adjacent cortex of inferior surface of the dominant left frontal lobe a theoretical cortical influence as an explanation for the ruptured esophageal complication was ventured. With our subsequent two cases and a brief survey of all our gastro-intestinal complications following intracranial surgery or trauma, and after some exploration into the literature on the subject, we concluded that alimentary-tract damage may occur following any craniotomy for cerebral or cerebellar disease. This conclusion led us to seek some solution or proposed treatment for such a rapidly fatal interruption in craniotomy convalescence. Prophylactic or preventive measures were considered, but without practical success and suggestions for active treatment of the condition were sought from our thoracic surgeon.

The essential information concerning each of our three cases is as follows:

Case 1—(NS 48240) March 10, 1948 Meningioma—Left frontal pole Female Age 35 years History of 12 months of headaches Advanced degree of increased intracranial pressure No localizing symptoms Ventriculography Left fronto-temporal craniotomy Decompression Death 36 hours after craniotomy Complete autopsy Ruptured esophagus

Case 2—(NS 471229) March 23, 1948 Supra-chiasmal adamantinoma History of 12 months of headaches Male Age 50 years No objective evidence of intracranial pressure Left homonymous hemianopsia Ventriculography Arteriography Right



A



B

PLATE I (A) Illustrating the extensiveness of the tear in the esophagus in Case 1, as viewed at the autopsy table. The forceps are inserted into the cardiac end of the intact esophagus.

(B) Autopsy specimen from Case 2, illustrating extensiveness of the esophageal rupture.

EMORY UNIVERSITY HOSPITAL
GRAPHIC CHART

RECORD NO 7007 U

NAME C. F. H. AGE 50 YRS SERVICE OR DOCTOR Neuro-Surg. 471229

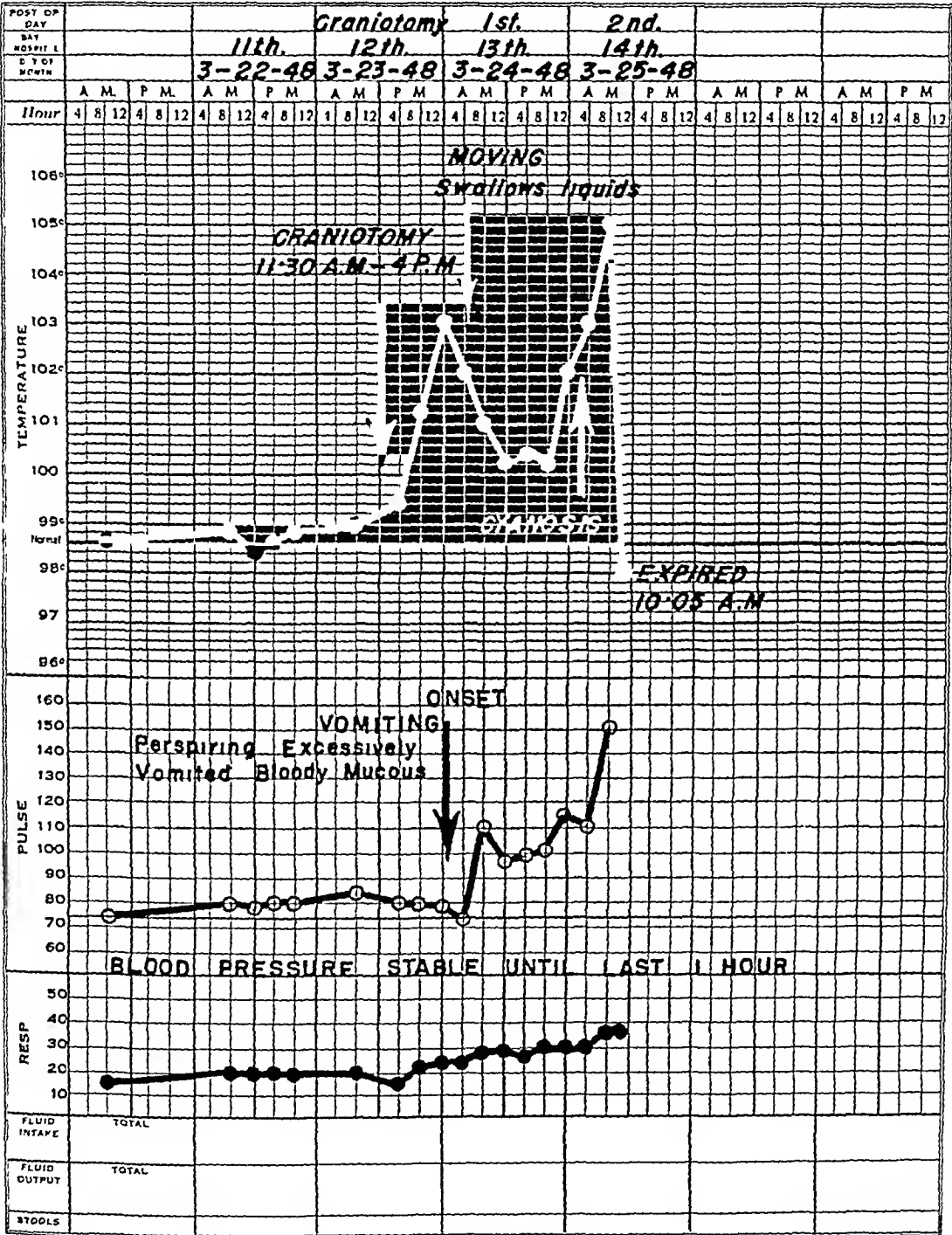


FIG 3 (Case 2) See text

EMORY UNIVERSITY HOSPITAL

GRAPHIC CHART

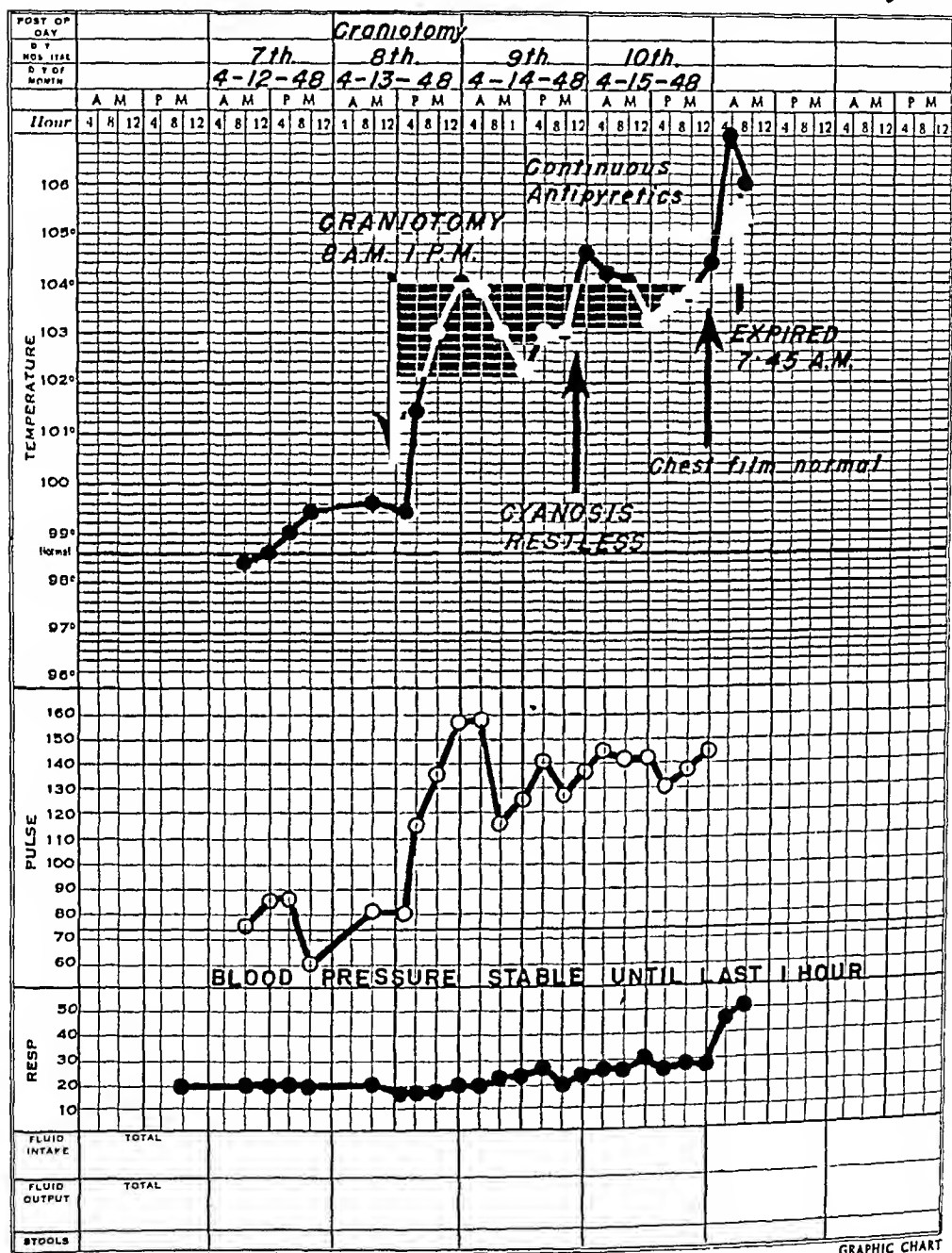
RECORD NO. *P.H. 100,986*NAME *W. H.* AGE *55 YRS.* SERVICE OR DOCTOR *Neuro-Surg. 48350*

FIG 4 (Case 3) See Text

temporo-frontal craniotomy Death 48 hours after craniotomy Complete autopsy Ruptured esophagus

Case 3—(NS 48350) April 13, 1948 Meningioma Left mesial sphenoid ridge Male Age 55 years History of 36 months of headaches Chronically increased intracranial pressure Semiconscious Ventriculography Left frontal craniotomy Death 56 hours after craniotomy Complete autopsy Ruptured esophagus

The histologic studies of our three tumors revealed that these growths were of a benign character, one being a polar meningioma of the left frontal lobe, the second a suprachiasmal adamantinoma situated posterior to the optic chiasm and grossly measuring less than two centimeters in diameter, the third lesion was also a meningioma, histologically more active than the first case, arising from the mesial limits of the sphenoid ridge. It is without the scope of this communication to discuss in detail the problems, neurologic, neurosurgical and histologic, involved in these cases. There were some diagnostic procrastinations and surgical blunders for which cognizant personal retributions have been made. Although 12 months or longer elapsed from the onset of intracranial symptoms in each case until a histologic diagnosis was established, it is not our opinion that the chronicity of the intracranial disease played any role in initiating the esophageal ruptures. A more important point for our presentation than symptoms, histology, personal mistakes or time elements is a reiteration of focusing attention on the cerebral territorial areas of our three efforts and the posterior fossa regions reported by Cushing, in which surgery was performed in an attempt to eradicate the intracranial disease. Remembering these territories, one might be more ready to recognize esophageal or alimentary complications should the postoperative convalescence of the craniotomy patient not continue satisfactorily.

It is our opinion that in our three cases the esophageal ruptures occurred before death and that the damage to this structure was neither the result of physical, mechanical trauma nor an exaggeration of postmortem changes in the alimentary mucosa so familiar to autopsy workers. In support of our ideas, none of our patients were intubated before or during their operative narcosis, none of the three were "tubed" or had any "aspiration efforts" postoperatively. All three patients vomited blood as the initial symptom. In the first patient, the retching and vomiting were both of such violence as to suggest a possible mechanical explanation for the rupture of the esophagus. Her initial vomitus before the addition of her violent retching contained blood, so the interpretation of this physical strain as a factor, after a study of the other two cases, was discarded. The histologic support of our antemortem concepts of the esophageal damage is summed up by the opinions of our pathologists in their report that "the microscopic studies of the alimentary perforations and the surrounding tissue changes are those of ante-mortem cellular activities and not postmortem tissue degenerative depictions."

The symptomatology of the esophageal ruptures in our three cases has been essentially identical. The postoperative symptom details recorded by Cushing in his two experiences could be substituted for any one of our cases. It is upon the appearance of these symptoms following craniotomy that we feel

the condition can be suspected. The confirmation of this suspicion by mediastinal aspiration constitutes a part of the proposed suggested treatment. The symptom complex can be summed up as beginning with vomiting, the vomitus containing blood, followed by a seething, restless irritability, respiratory difficulties, sweating, cyanosis and a progressive loss of consciousness, an increasing pulse rate, an uncontrollable hyperthermia, profound coma and rapid death.

The immediate postoperative reactions of our patients to the craniotomy were satisfactory in all three instances. The pulse rates, blood-pressure recordings, temperatures and respirations were within expected postoperative ranges. These "vital signs" recorded at 15- and 30-minute intervals remained rather stationary during the first 24-hour period after operation. The vomitus, produced in the first 8 to 12 hours after conscious activities, appeared following recovery from the "anesthetic hypnosis," consistently contained blood, either as "coffee-ground" watery fluid or bright-red bloody mucous material. The vomiting continued through conscious and semiconscious periods. After the first postcraniotomy 24-hour period, such consciousness as had been regained began to lag and the patients lapsed into a stupor which progressed to a coma within from four to six hours. With the initial regression of consciousness, extreme restlessness and excessive sweating developed. In this same 24-hour period, with the reduction in conscious contacts with the patient, cyanosis was definite in the finger tips and mucous membranes. With the appearance of cyanosis, the pulse rate increased to 120 per minute and higher. This rapid rate was maintained almost until death. The immediate temperature elevation that usually characterizes every craniotomy having begun a descent to more normal levels at the beginning of the first postoperative day, rather abruptly became elevated and continued to do so. This occurred despite therapeutic efforts that in most instances have been effective in controlling postcraniotomy hyperthermias. The pulse-rate increase was concomitant with the temperature elevation. The temperature continued to rise until a few minutes before death when an abrupt drop to normal or subnormal figures was recorded. A change in the respiratory rate developed, with the appearance of cyanosis in the extremities. This rate remained elevated in two of the cases. An hour before death in one patient, this rate dropped to 6 to 10 per minute. The excursions of the thoracic cage were in each case rather shallow and became more so as the rate increased. Throughout the postoperative course our three patients maintained an essentially normal blood pressure.

Just before death, there was an abrupt drop in pressure to levels which could not be recorded and there was no response whatsoever to so-called "cardiac" or "shock" therapeutic efforts. Other than the secondary lapse of consciousness, none of our patients exhibited any new objective neurologic symptoms in the postcraniotomy course. With our already described alterations in "vital signs," in Cushing's two experiences there is no description of his patients' developing new neurologic symptoms in the nature of pupillary or reflex changes, spasticities or any phenomenon to suggest added cerebral disturbances. There was no objective evidence in his or our patients suggesting a general acutely increasing intracranial pressure. There were no new cerebral

manifestations of a localizing nature during the time we have designated as the one in which the esophageal damage and systemic tissue reactions were active

In a review of seven postcraniotomy postmortem examinations, all performed for traumatic or neoplastic conditions, the clinical developments within the first 24 to 36 hours after operation lead us to believe that these deaths may have been the result of pathologic developments in the alimentary tract and not primarily the result of intracranial complications. In these cases, autopsy studies were "limited to the head only," and while the deaths were ascribed to pathologic changes in the brain and to the operation, the gross and microscopic appearance was not in every instance a completely satisfactory explanation of the postoperative death. There have been seven other deaths in our experience in which the clinical developments were consistent with a lesion of the upper gastro-intestinal tract. Unfortunately, autopsies could not be obtained in these cases. It is our opinion that our earlier inference of the rarity of alimentary-tract complications from neurosurgical efforts is more relative than real. Obviously only complete autopsies will reveal the true frequency and establish the incidence for this cause of death as an aftermath of cerebral operations.

Our interest in seeking help for the diagnosis and treatment of esophageal damage following intracranial surgery was prompted by the fact that our three cases occurred within a few weeks of one another. The secondary reason for eliciting some help for the complication was based on the opinion that the situation is more frequent than is suspected. This idea developed after a critical review of the clinical charts of the 14 unsatisfactorily explained "cerebral deaths" following craniotomy. There are no intimations in the literature concerning treatment or diagnosis of the gastro-intestinal complications secondary to craniotomies. Since it is not specifically established that the pathologic physiology of these esophageal disruptions is primarily vagal or celiac dysfunction, or an imbalance between these two autonomic alimentary innervations, one cannot as yet offer specific prophylactic measures. There are no pharmacologic preparations which will totally paralyze the vagus nerve and there is no justification or practical need for surgical attack on this structure or the celiac sympathetics preliminary to a craniotomy. Our immediate possible solution for establishing the diagnosis and for active treatment for the insult to the mediastinal tissues was suggested by Dr. Osler Abbott of our thoracic-surgical service.

The proposal of Doctor Abbott is that when an esophageal rupture is suspected, a bedside roentgenogram of the chest be made. The presence of mediastinal air depicted on this film would confirm one's clinical suspicions. His next suggestion is that a Levine tube be inserted into the esophagus. If blood be obtained on aspiration, iodized oil should be injected into the tube and a second roentgenogram of the chest be made. A diffusion of this contrast media into the mediastinal spaces would confirm the diagnosis. After the establishment of the diagnosis, some benefit might be obtained by surgical drainage of the territory. This could be accomplished by the insertion of an intercostal tube, or perhaps more effective drainage would be secured by a resection of the proximal portion of a rib. This would be followed by a nasal tube into the

stomach to assure continued removal of gastric contents. It is likely that this emergency surgery would have to be performed without transfer of the patient to the operating theater. The definitive plastic repair of the esophagus could be performed as a later elective procedure. Antibiotic administration and chemotherapy would constitute a part of the systemic treatment. An interval gastrostomy should be considered if the patient responded satisfactorily to the mediastinal drainage. This plan of treatment appears drastic and certainly would require surgical fortitude. Pulmonary embolectomy and vena-cava ligations for general surgical complications are also bold procedures. The removal of a benign brain tumor complicated by such a rapidly fatal sequel as an esophageal rupture would, in our opinion, justify any procedure offering hope of saving a life. Should the symptoms in any of our future craniotomies lead us to suspect damage to the upper alimentary tract, the diagnostic and therapeutic efforts outlined above will be promptly instituted.*

SUMMARY

A disturbance of body thermal reactions following certain craniotomies and high cervical laminectomies is a condition commonly witnessed and expected by neurosurgeons. These hyperthermias are usually explained on the theory of damage to the "heat-regulating centers" or on the basis of a disturbed peripheral circulation. Extreme changes in pulse, respiratory rate and the appearance of cyanosis following intracranial surgery are symptoms too frequently attributed to altered cerebral functions. Vomiting, common in post-operative craniotomy patients, is accepted as an anticipated postanaesthetic or intracranial reaction. Should this vomitus contain blood, the physiologic alterations which simulate the symptoms of intracranial complications must be properly evaluated in order to recognize an alimentary lesion. It is felt that the characteristics of an esophageal rupture following intracranial operations can be recognized by careful study of the clinical chart even if there are no additional neurologic developments other than an interference in consciousness.

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DISCUSSION.—DR CHARLES BAGLEY, JR., Baltimore. Doctor Fincher has reported a most interesting and, I think, unrecorded experience. I would like to report a similar experience. A 43-year-old male came to Mercy Hospital, Baltimore, because of severe and frequent epileptic seizures. He also gave a history of gastric symptoms which had been determined to be the result of a gastric ulcer. The gastric symptoms and cerebral

* Dr Osler Abbott performed the proposed plastic operation on a ruptured esophagus of neurogenic origin in an adult male on January 6, 1949. This patient is still living April 20, 1949.

symptoms extended over a long period. An encephalogram, usually a mild procedure, was done with negative findings and, following this, vomiting was very troublesome. Forty-eight hours after the procedure there was sudden onset of severe abdominal pain. The patient died within 24 hours and an autopsy revealed a perforated gastric ulcer.

DR ROY D. McCLURE, Detroit. I was intrigued by the title of this paper—"Esophageal Rupture as a Complication of Craniotomy" and I would like to mention a patient I had when I was resident at Johns Hopkins Hospital, who had a rupture of the stomach as a complication of craniotomy.

In 1907 Dr. Harvey Cushing had sent me to New York to work with Dr. Alexis Carrel to learn his technic of blood vessel suture. I also learned there, from Dr. S. J. Meltzer and Dr. J. R. Auer, this method of intratracheal anesthesia which completely replaced the cumbersome Sauerbruch chamber we were using previously. We came back and began using tracheal anesthesia. While I was resident Dr. Walter Dandy was first assistant, and at that time was becoming more and more interested in brain surgery. When this patient came in it was decided that the gasserian ganglion should be removed. A member of this Association—not present at this meeting—gave the intratracheal anesthetic to the patient. In those days we did not have operating tables with wheels or castors. The patient was anesthetized on a stretcher by this doctor, whose name I won't mention, and brought into the operating room. Orderlies at that time lifted the patient off the stretcher, up against their abdomen and chest, the stretcher was withdrawn and the patient was laid on the table. I was going to help Walter with the operation. We noted after the patient was draped that she was getting very blue and was having trouble with breathing. We immediately took off the draperies and noted that she was tremendously distended. We passed a stomach tube and got a good deal of gas from the stomach. We knew then that the anesthesia tube was in the esophagus and not in the trachea. Her condition did not improve and we put her in the anesthesia room for a couple of hours. The liver dullness had disappeared. Then the blood count had started up so we decided there must be a ruptured viscus. I operated on her and found a large quantity of air in the abdominal cavity and a rupture in the lesser curvature of the stomach near the esophagus. The rupture was not directly through, like that produced by ulcer. We inverted the rupture in the stomach and sutured with mattress sutures and had a very prompt recovery.

The only reaction we had in this patient was that, when we made ward rounds every day, she complained—"Doctor, I wanted my head operated on, not my stomach." Within ten days Dr. Walter Dandy did do the gasserian ganglion operation and she made a complete recovery and left the hospital. For perfectly obvious reasons we did not report this complication at that time.

I am indebted to Dr. Alfred Blalock for supplying me with an abstract of this history at this time.

DR COBB PILCHER, Nashville, Tenn. Doctor Fincher's paper is a very important contribution, not only because it calls attention to a fortunately rare but usually fatal complication in otherwise successful intracranial procedures, but because it suggests the possibility of complications of this character which do not terminate fatally and may occur much more frequently than we think. I say this because it is not particularly uncommon, in patients who have had operative procedures in this region of the brain and who remain in a state of so-called pathologic sleep for some time after operation, for them to vomit, always in the past considered to be post-anesthetic vomiting, and it is not particularly uncommon for the vomitus to contain blood. We have always tended to lay this in the lap of the anesthetist and assumed it was due to manipulation associated with insertion of the intratracheal tube, we have even criticized the anesthesia department rather severely for this at times, and Doctor Fincher's contribution makes one wonder if perhaps we have not been overlooking non-fatal, non-perforating esophageal or gastric complications similar to those he has mentioned but not progressing so far.

DR HUGH A GAMBLE, Greenville, Miss I have never seen a case of esophageal rupture secondary to a craniocerebral injury. However, I wish to report a case of acute pancreatitis which came on shortly after sustaining a fracture of the skull over the right frontal region.

This patient was employed at a sawmill, and while working around the boiler was struck upon the front of the skull by a flywheel causing a compound depressed fracture on the right side. He was temporarily unconscious and was brought to the hospital at 10 00 A. M., at which time he had regained consciousness. An exploration of the wound was done. There was no cerebral hemorrhage. A depressed fracture was elevated. The wound was sutured and drained. About three hours later he began to suffer excruciating epigastric pain. He gave a history of having had an operation about five years before for intestinal obstruction and it was thought that possibly there had been a recurrence of this condition. The pain was unremitting in character and unrelieved by opiates. At 5 00 P. M. he was again taken to the operating room, the abdomen was opened and it was found that he had an acute pancreatitis, the pancreas being about twice normal size and all the surrounding tissues markedly edematous. The pancreas was drained through the gastro-hepatic ligament and a cholecystostomy was also done. The patient made a good recovery.

The owner of the sawmill carried insurance and the company made inquiries as to whether or not the acute pancreatitis had any connection with the original injury. I told them that in my opinion it was simply a coincidence, but from what I have heard this morning I feel that I must have been mistaken in that viewpoint and that there was a definite connection between the two.

This paper is of great importance to the general surgeon. It has brought out the complications that can ensue from cranial injuries and cranial diseases, to which we have not paid particular attention in the past.

DR EDGAR F FINCHER, Atlanta (closing) I want to thank Doctor Bagley, Doctor McClure, Doctor Pilcher and Doctor Gamble. I would be interested in Doctor McClure's experience with Doctor Dandy, for I am sure that in those days Doctor Dandy was doing the transtemporal approach to the section of the posterior root of the fifth nerve. In his latter years when he exposed it by way of the posterior fossa he uncovered a good many tumors. It is possible that the patient described by Doctor McClure may have had a neoplasm.

I had hoped that Doctor Swanson, my associate, who covered all the literature—and I assure you that it is voluminous, both experimental and clinical—would present some of this pertinent information. I do not believe the influence of the central nervous system on alimentary lesions is well appreciated unless one does go through the literature, particularly the experimental material.

TREATMENT OF HYPERTHYROIDISM IN CHILDREN*

JOHN H LYONS, M D

WASHINGTON, D C

THE PURPOSE OF THIS PAPER IS TO DISCUSS THE TREATMENT OF HYPERTHYROIDISM IN CHILDREN AND TO REVIEW THE CASES OF THIS DISEASE AS OBSERVED AT THE CHILDREN'S HOSPITAL OF WASHINGTON, D C, WITH REFERENCE TO OTHER SERIES

Hyperthyroidism is a rare disease in children, especially in the very young. It has, however, been diagnosed in infancy, Klaus¹ having reported the case of a nine-month-old baby, and White² an even more unusual instance of hyperthyroidism in a male fetus. Its frequency rises with increasing age, reaching a maximum at the time of puberty. In the past 13 years only eight children with the disease have been admitted to the Children's Hospital in Washington, D C. During the same period there were 78,659 admissions in all, therefore the incidence of hyperthyroidism was slightly more than 0.01 per cent. While this is much lower than the figures presented by some medical centers where a large amount of thyroid surgery is done, it is in keeping with those from other pediatric services. Schwartz³ stated that on the pediatric service of the Western Pennsylvania Hospital in Pittsburgh, where there were approximately 1,000 admissions a year, in a 20-year period there was only one case of exophthalmic goiter in a child, and at Long Island College Hospital in 1,000 operations for exophthalmic goiter only four were on patients who had not yet reached puberty. The age limit at the Children's Hospital in Washington, D C, is 12 years, while the bulk of cases reported in the literature are among the 13- and 14-year-olds, many of whom probably should not be classified as children. In Dinsmore's⁴ series of 57 cases 65 per cent were between 12 and 14 years old. Incidentally, the increase in thyroid activity during pubescence makes it difficult to draw the line between the normal and the abnormal.

Hyperthyroidism is especially rare in male children. The ratio of females to males varies widely in different series, being 16 to one in Bram's⁵ series of 128 cases, and three to one in Kerley's.⁶ Kennedy⁷ reported a ratio of approximately seven to one in 157 cases at the Mayo Clinic.

No more is known about the etiology of hyperthyroidism in children than in adults. Pierce⁸ dismissed the subject by saying that no definite etiologic agent was known. While this is true in a strict sense, certain predisposing or exciting factors are recognized and must be given consideration. There is evidence that heredity may play an important part, as in the family reported by Clumenko and cited by Dinsmore,⁹ in which the mother, two daughters, and a child of each daughter, one a boy and the other a girl, had the disease. In some cases hyperthyroidism seems to follow infectious disease, and occasionally psychic trauma has appeared to be the causative agent. Bram⁵ stated that rare incidence of psychic trauma as a factor in children is in direct contrast with the history of the disease in adults, in whom psychic trauma appears to be of

* Read before the Southern Surgical Association, White Sulphur Springs, W Va, December 7, 1948

great significance Edgien¹⁰ called attention to the striking frequency with which an infection seemed to be the precipitating cause of hyperthyroidism in the young. The question has been raised frequently in the past as to whether the widespread use of iodine in children to prevent endemic goiter may not occasionally be the cause of exophthalmic goiter. Recent investigations suggest that some goitrogen in food or drugs may be responsible.

A very important point is that the hyperfunctioning thyroid gland in children practically always manifests diffuse hypertrophy and produces the same clinical picture, namely, exophthalmic goiter. No case of adenomatous goiter with hyperthyroidism has ever been seen at the Mayo Clinic.¹¹ The gland is moderately and rather symmetrically enlarged and is usually firm in consistency throughout its entire substance. Microscopically, the gland shows diffuse parenchymatous hypertrophy and hyperplasia. The normal low cuboidal cells of the follicular epithelium are replaced by high cuboidal or columnar cells, and the epithelium manifests infoldings and papillary projections into the acini. The iodine content of the gland is greatly reduced.

The symptoms of hyperthyroidism in children are analogous to those in adults with exophthalmic goiter. The onset may be gradual or sudden, with nervousness or irritability frequently the initial symptom. Sometimes a teacher is the first to detect that the child is ill because of deterioration in his school work. Tachycardia, exophthalmos, goiter and tremor are almost constantly present. Other symptoms are increased appetite, heat intolerance, sweating, increased pulse pressure, weakness, loss of weight, dyspnea and gastro-intestinal disturbances. The pulse rate may be as high as 180 per minute, and the systolic blood pressure may rise to 190 mm Hg with no increase in the diastolic pressure. Thrills and bruits can often be detected over the gland and heart. Several authors have reported skeletal development exceeding that which is normal for the patient's age, and others have mentioned delayed or diminished sexual development. When these children grow unusually rapidly, their heights ultimately are not greater or less than the average.

Although the disease is usually severe in children, crises do not occur as frequently as in adults. The course of the disease is characterized by periods of remission and exacerbation, and in rare instances it is self-limiting. The longer the duration of the disease, the more deleterious are its effects upon the child.

It is evident that the early diagnosis of a condition in which profound metabolic and nervous disorders are present is of the greatest importance. Nevertheless, while the clinical picture of hyperthyroidism in children is typical, the diagnosis often is not made until late in the disease, probably because the condition is so rare that the clinician is slow to consider it as a possibility. The determination of the basal metabolic rate, so useful in diagnosis in adults, is of questionable value in a nervous and often unco-operative child. Lahey¹² has recommended a method of determining the basal metabolic rate developed by Bartels. He has found that under pentothal anesthesia falsely elevated rates are not obtained. This method should prove useful in children. Blood-choles-

terol determinations are of limited value. A high result rules out hyperthyroidism but a low reading is not a reliable confirmatory sign. In the absence of dependable laboratory data, the diagnosis must rest on the history and physical findings.

For many years subtotal thyroidectomy has been the generally accepted treatment for hyperthyroidism, even though it has been recognized that this procedure, while giving symptomatic relief, does not correct the primary underlying cause. There is disagreement as to the amount of thyroid to be removed in a child, and also as to the frequency of persistent hyperthyroidism and myxedema after operation. Welt¹³ stated that very wide thyroidectomies are necessary in children and can be expected to yield, in general, better results than in adults. Welt¹³ and Nixon,¹⁴ citing Means,¹⁵ favored thyroidectomy at least as radical as in adults, because of the high rate of recurrence and persistent hyperthyroidism in children. Cattell,¹⁶ Dinsmore⁴ and Abbott,¹⁷ on the other hand, emphasized the frequency of myxedema postoperatively, but Kennedy⁷ stated that postoperative myxedema rarely occurs. It is probably true, as Pemberton and Black¹⁸ have stated, that relatively the same amount of thyroid tissue should be removed in a child as in an adult. Recurrence or myxedema is not an uncommon postoperative manifestation, but, according to these authors, there is no indication that the preservation of more or less of the gland would give more uniform results.

Before 1923 the operative mortality in children with hyperthyroidism was about 9 per cent. This rate was achieved by careful preoperative preparation and multiple-stage operations. After Plummer introduced the use of Lugol's solution as part of the preoperative treatment in 1923, the operative mortality dropped to approximately 2.5 per cent without resort to multiple-stage operations.

Without dwelling on the involved and obscure nature of the pathologic physiology in exophthalmic goiter, it should be mentioned that the beneficial effects of the administration of iodine in this condition are probably due to inactivation of the thyrotropic hormone, which in turn produces a lowering of the basal metabolic rate, an amelioration of symptoms and regression of the pathologic process in the thyroid gland. Means¹⁵ found that the fall of the basal metabolic rate averaged 3.5 points a day on adequate iodine medication. The regressive changes in the gland consisted of reduction of hyperplasia and increase of colloid. While the effects of iodine in exophthalmic goiter are most striking, it was never seriously considered as a substitute for surgery but only as a means of making surgery less dangerous.

The introduction of thiouracil by Astwood in 1943 aroused the hope that this drug might prove a welcome substitute for surgery in the treatment of hyperthyroidism. The pediatric literature abounds with statements expressing this hope and emphasizing the importance of avoiding any actual loss of the substance of the gland, because the future growth and development of the child are so dependent on thyroid activity. The implication of these articles was that children who have had subtotal thyroidectomy do not develop normally, but this is not borne out by the facts.

Since the introduction of thiouracil several other thioureas have been tried in the treatment of hyperthyroidism. All are capable of reducing the basal metabolic rate to normal if given in sufficient quantity and of producing myxedema if given in large enough doses over a long period of time. According to various authors, the rate is reduced from 12 to 0.5 per cent each day. The rate of reduction is influenced by the type of hyperthyroidism, the duration of the disease, whether or not the patient has been on iodine and the geographic location. These drugs act by inhibiting the production of thyroxin. They probably also stimulate, either directly or indirectly, the production or liberation of thyrotropin by the pituitary gland, which accounts for the hyperplasia in the thyroid—always present when these drugs have been administered for any length of time. In other words, these drugs reduce the basal metabolic rate to normal and ameliorate the symptoms but they do not change the histopathologic picture, the gland remains diffusely hyperplastic, and resection of such a gland is most difficult because of friability, uncontrollable bleeding and difficulty of exposure. These disadvantages can be corrected by administration of iodine with the thiourea.

Propyl thiouracil is the least toxic of the thiourea derivatives that have been elaborated, but even it cannot be used without risk. All of them are capable of causing fever, rash, leukopenia, agranulocytosis and even death. Gargill¹⁹ found toxic symptoms in 15 per cent of 6,800 patients with hyperthyroidism treated with thiouracil, and the reports of Reveno,²⁰ Bartels,²¹ Crile,²² Astwood and Van der Laan²³ include 494 cases of hyperthyroidism treated with propyl thiouracil with toxic symptoms in 1.2 per cent.

Another objectionable feature of these drugs is their possible carcinogenic action. The hyperplasia which they produce in the thyroid gland approaches malignant change. Gorbman,²⁴ after prolonged feeding of thiourea to mice, found thyroid cells in the veins of the thyroid gland and small islands of thyroidlike cells in the lungs. These aberrant cells showed many mitotic figures.

The hope of the pediatricians that thiouracil, or the safer propyl thiouracil, would prove a substitute for surgery has not been realized. In the first place, when basal metabolism has been reduced to normal and the drug discontinued, hyperfunction of the gland will usually recur after a variable period. This is to be expected, since the diffuse hyperplasia present in the gland has not been reduced by the action of the drug. There are too few reports of treatment of hyperthyroidism in children with thiouracil or propyl thiouracil on which to base an opinion, but the rate of relapse in adults after discontinuing the drug has been reported to be from 20 to 80 per cent, and there is no reason for believing it would be lower in children.

Control of hyperthyroidism by continuing to administer thiouracil or propyl thiouracil indefinitely is certainly not to be recommended. Prolonged treatment with these toxic drugs may cause the child to develop into a neurotic unstable individual, furthermore, it exposes him to the risk of drug fever eruptions, leukopenia, agranulocytosis and even death.

There have been very few reports of the treatment of hyperthyroidism in children by irradiation. Rose, Rose and Pendergrass²⁵ reported ten cases with

failure in two. This form of treatment has had an extensive trial in adults and has been largely abandoned and would in all probability be no more successful in children than in adults.

Radioactive iodine is the most recent therapeutic agent to be tried in thyrotoxicosis, but its use in children must be condemned for several reasons. In the first place, this form of treatment is followed too frequently by myxedema. Haines,²⁶ at the meeting of the American Goiter Association held in May, 1948, reported 35 cases of exophthalmic goiter treated with radioactive iodine. Myxedema developed in five. It is not known definitely whether or not the gamma rays that are introduced are carcinogenic, or what their effect may be on other parts of the body, notably the kidneys. Mayo Soley,²⁷ at the same meeting, stated that it may be as much as 25 years before the end results of treatment of exophthalmic goiter with radioactive iodine are entirely known.

Because of the failure of thiouracil and related drugs to live up to the expectations of the pediatricians, the uncertain results of roentgenotherapy, and the dangers associated with the use of radioactive iodine, subtotal thyroidectomy remains the best treatment for hyperthyroidism in children. Careful preparation must precede operation if it is to be carried out with safety, and the problem of preparing children is different from that in adults. In the latter, hyperthyroidism may be associated with diffuse hypertrophy or with adenomatous goiter, but in children it is always associated with diffuse hypertrophy. Fortunately, it is this type of hyperthyroidism which responds best to iodine.

In recent years, because of the intense interest in thiouracil and related drugs, and the enthusiasm over the possibility of these drugs supplanting surgery, we have overlooked the great value of iodine in preparing patients with hyperthyroidism for operation. It has been largely replaced by propyl thiouracil but is still used to prepare the patient with a mild form of the disease and is administered in more severe cases after propyl thiouracil has brought the basal metabolic rate to normal, or in conjunction with propyl thiouracil throughout preoperative treatment to make operation less difficult and less dangerous.

It is my firm conviction that iodine is the drug of choice in preparing children with hyperthyroidism for operation and that propyl thiouracil should be used only in those cases in which iodine fails to reduce the basal metabolic rate and allay the symptoms so that a single-stage thyroidectomy can be carried out safely. There are three reasons for my conviction: first, the type of hyperthyroidism always present in children, namely diffuse hypertrophy, responds especially well to iodine; second, the child can be much more rapidly prepared for operation with iodine than with a thiourea derivative; and third, iodine is a safe drug, while thiouracil and even propyl thiouracil are potentially dangerous.

The number of cases of hyperthyroidism treated at the Children's Hospital in Washington, D. C., in the last 13 years has been small (eight). However, the fact that this number represents all the patients with this condition admitted

to one of the largest children's hospitals in this country within a considerable number of years should furnish justification for summarizing them briefly. The ages of the eight patients were as follows: one 12 years old, one 11, two 10, and one 9, one 8, one 3 and one 2. Six of the eight children were females, two were males, four were white, three were Negro and one was Chinese. The relatively large number of Negro children in this series is in contrast to Dinsmore's series of 57 which included only one Negro child.

All the patients presented the picture of severe hyperthyroidism on admission in spite of the fact that all of them had been under treatment before coming to the hospital. For the eight children the average pulse rate was 132 per minute, their average basal metabolic rate was plus 39, and their average blood cholesterol was 161 mg per cent.

One of the patients, the Chinese girl, who was two and a half years old, died in thyroid crisis 22 hours after admission. One child was kept in the hospital long enough to complete a diagnostic study, but then was discharged because of a measles quarantine. She was to return for treatment later but failed to do so. Another patient was treated with propyl thiouracil for one year and did not come to surgery.

The other five patients were operated on without mortality. Four were prepared with iodine, to which they responded well, and then went through operation satisfactorily. The preoperative preparation of the remaining patient, a three-year-old white girl, was started with propyl thiouracil. This, however, had to be discontinued in two weeks as a rash appeared and her white-cell count dropped to 2,000 with 2 per cent polymorphonuclear leukocytes. The patient was then given Lugol's solution and three weeks later a subtotal thyroidectomy was carried out successfully.

Of the six patients who were treated at Children's Hospital, five with subtotal thyroidectomy and one with thiouracil, five are still alive. One boy on whom thyroidectomy was performed at ten, died suddenly six years later while apparently in excellent health. The coroner gave as the cause of death, "acute congestive heart failure and chronic endomyocarditis."

The five living patients who received treatment were brought back to the hospital recently for physical examination and estimation of basal metabolic rate, their histories were also brought up to date. The four on whom subtotal thyroidectomy had been performed had remained well since operation and none showed any symptoms of hyperthyroidism. The basal metabolic rate was normal in every case. Physical examination revealed that the eyes of all of them were a little larger than normal and that two of the four had a slightly increased amount of body hair. Two of the girls had attained the age of puberty and both had normal menstrual histories and one had married and had a normal baby.

The girl who had been treated with thiouracil is now 15 years old. She is apparently well developed, with normal eyes and no increase in body hair, but her menstrual flow has been excessive at times, and four basal metabolism tests yielded rates between minus 17 and minus 28.

This small series offers further evidence that preoperative preparation with iodine and subtotal thyroidectomy constitute the most satisfactory treatment of hyperthyroidism in children. No child so treated, even after an interval of many years, has symptoms of either hyperthyroidism or myxedema. One child reacted unfavorably to propyl thiouracil used preoperatively, another, whose hyperthyroid symptoms responded to thiouracil has since become myxedematous and has menstrual difficulties. The results of treatment in this series are in general agreement with those of more extensive series in the literature and justify the opinion, which I hold, that subtotal thyroidectomy preceded by administration of iodine is the safest and most successful procedure for hyperthyroidism in children.

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DISCUSSION —DR RICHARD B CATTEN, Boston Doctor Lyons was kind enough to send me his paper in which I was very much interested. He has raised a number of points with which I have only minor disagreement. In the first place, we might quote the incidence of hyperthyroidism in children in a little different way. He quoted it as 0.001 per cent of all admissions to the Children's Hospital. In our clinic, of all patients coming to us with hyperthyroidism, approximately 1 per cent are children 13 years of age or younger. It is quite important, I think, in quoting series, to be sure that the age limitation is quoted, because the incidence at age 14 and 15 is considerably above that.

I reported our cases from the Lahey Clinic in 1933, and Doctor Hursthal of our medical department told me recently that we had had somewhat in excess of 150 of these patients under 13 years of age before 1943. Since that time, as you know, Astwood introduced the use of the antithyroid drugs, and Doctor Bartels has recently reviewed our first series of 1000 patients with hyperthyroidism prepared with these antithyroid drugs, between May, 1943, and October, 1947 (the number now is in excess of 1500). During this time there were 12 patients in 1000 who were 13 years of age or younger with hyperthyroidism. Doctor Lyons has called attention to the fact that nowhere in the literature is there a report of a patient with hyperthyroidism without hyperplastic or exophthalmic goiter. We have one such patient, previously reported by Doctor Bartels, a child born a cretin with a nodular goiter who, at the age of 9, developed hyperthyroidism and now is in total myxedema controlled by thyroid extract.

The diagnosis of hyperthyroidism in children is the same as in adults, and all we need do is think of the diagnosis as a possibility in children. But may I call attention to one feature which is frequently missed in consideration of this problem, that is, the problem of growth. In most papers on this subject the question is raised of leaving enough thyroid to make possible normal growth, but we must not forget the fact that in the presence of hyperthyroidism the rate of growth between the ages of 9 to 13 is two to three times that in the normal individual. If you wish to treat patients with hyperthyroidism during this age period by conservative medical measures you will have some "giants" in the family that you would not otherwise have had. This question of growth, and rapid growth, particularly the closing of the ossification centers at an early period, is an important consideration in deciding whether to treat them medically or surgically.

Of our first 150 patients, only one died—that was a first stage operation more than 20 years ago—and I believe the reason for the low mortality was Doctor Lahey's insistence that stage operations be done. That problem has now changed, and in this we disagree somewhat with Doctor Lyons' conclusions. He has said there are three reasons for the use of iodine and subtotal thyroidectomy, good response, more rapid response and safety. To be sure, the use of propylthiouracil is dangerous unless carefully controlled. The incidence of reactions to this drug in our cases as reported by Doctor Bartels is 12 per cent. Seven of our 12 patients were prepared with thiouracil, and 5 with propylthiouracil, but there were no reactions in this group.

I would like to point out that those children prepared with iodine alone have rapid pulse rates that are alarming, they perspire freely and use a large amount of oxygen. Why not utilize this drug that has been well demonstrated to reduce the toxicity of the

patient to a nontoxic state, so that subtotal thyroidectomy can then be performed with the greatest of safety? The 12 patients I am reporting were operated upon without mortality

DR T C DAVISON, Atlanta This to me is a most interesting subject, as I have had some experience with children with hyperthyroidism I wish to present a case on which, fortunately, I have preserved the stages of the child's development in photographs

Slide No 1 shows a child aged 7, with marked exophthalmos and a small goiter This child was seen by me when I was in the home to see the mother who had gallstone colic At first glance I said to the mother—"Your child has a goiter" She said, "Yes, I know she has" She was under treatment by a prominent pediatrician whom she mentioned I should have stopped there, but I asked what was being done for her He was giving her iodine, and I asked how much "Five drops, three times a day" "How long has she been taking it?" "A year and a half" "When did he see her last?" He had seen her only once and failed to tell the mother to bring her back to see him or to tell her when to stop the treatment

I think this child's hyperthyroidism, and the hyperplastic thyroid gland, was due to too much iodine over a too long period of time I think this would come under the head of "the use and abuse of iodine" This child probably had a congenital goiter, I do not know what type, but when I saw her she had a typical hyperplastic hyperthyroidism with exophthalmos, she was nervous, couldn't sit still, and the teacher had sent her home from school because she was too nervous to be in school

After I had operated on the mother for gallstones, I took the child in hand She was a typical hyperthyroid with a pulse of 140+ This graphic chart which is dated 1922—26 years ago when the child was 7—shows the basal metabolism to be +40, she couldn't sit still and she acted like a bug on a hot stove I stopped the iodine for three months and then started her back on it again to reduce her toxicity Iodine was the only antithyroid available at that time as we did not have the thiouracil drugs then I then operated and removed what I considered to be approximately 75 per cent of the hypertrophied, hyperplastic thyroid gland This is very important, gentlemen, do not ever remove too much thyroid gland in a growing child The thyroid gland is necessary for growth, and remember that this child's gland had been stimulated by too much iodine over a too long period of time, whipping it up and fanning it into a flame resulting in a hyperplasia and thyroid toxemia I left what I estimated to be 25 per cent of the gland and this next slide shows the child six months after operation I believe that portion of the gland which I left underwent atrophy and the child gradually became myxedemic Now, looking at this picture we can see slight evidence of beginning myxedema, but I did not detect it at that time She had just passed her eighth birthday, she looked pretty well, and the family was apparently happy with the result I lost sight of her for several years, or until she sustained a fracture of the leg and I was called to see her, and I received a real shock to see such a change in the child

This next slide shows a typical picture of myxedema You would hardly believe this was the same little girl shown in the previous pictures Notice the full round face with no expression, the coarse straight hair, the dry skin, and the thick neck like a Jersey bull's neck She was not doing well in school She had grown very little in height, but had become very fat, and the family thought it perfectly natural for her to be this way I was distressed and, after treating the fractured leg, I made an agreement with the mother that if she would bring the child to my office once a month for the next several years I would make no charge for it

I put her on thyroid extract and this next slide shows the child one year later In one year's time she gained five inches in height, lost 19 pounds in weight, developed secondary sex characteristics, began menstruating and passed two grades in school in one year I may have underestimated the quantity, but I was sure that I had left 25 per cent of the gland, but I did not count on that portion of the gland which was left undergoing atrophy

In treating adults for exophthalmic goiter I frequently remove the entire gland, as an adult needs very little thyroid tissue and can usually do without any, and we seldom see myxedema develop. We often see myxedema in individuals who have never had thyroid surgery.

I have operated on other children for hyperthyroidism and left approximately 25 per cent of the gland, and in some cases the child either did not fully recover from the symptoms or shortly thereafter developed recurrence of symptoms. In a true case of hyperthyroidism the entire gland is involved and when you leave 10 or 25 per cent of the gland you have left the patient just that much hyperplastic tissue and you are almost certain to have a recurrence of symptoms.

I have recently operated on one patient the second time, after a period of four years. I had operated the first time when she was 12, leaving approximately 25 per cent of the gland, she never fully recovered and I had given her thiouracil for a year and then lost sight of her. Her physician sent her back to me when she was 16½, with recurrence of all her symptoms, marked tachycardia, an enlarged heart with decompensation, she was so ill that she could not attend school. After proper preparation I did a total thyroidectomy.

This last slide shows the first patient as a young lady, now grown, and you will notice from the ring on her finger that she is married, and she now has a child of her own.

DR FRANK H LAHEY, Boston. I would not inflict two people from the same clinic on you if I did not want to bring something to you which I think is of value in the problem of managing patients with hyperthyroidism with the antithyroid drugs. We are going to have to use these antithyroid agents on children as well as on adults, and in children as well as in adults there will be a group of patients who are sensitive to these agents. For this reason I wish to review our experience with alternate drugs in patients who are sensitive to any one of the antithyroid agents.

We now have in the clinic five agents available to bring the metabolism to normal in patients with hyperthyroidism. We have thiouracil in 600 mg doses, we have propylthiouracil in 200 mg doses for primary hyperthyroidism and 300 mg doses for toxic adenoma, we have methylthiouracil in the same doses, we have aminothiazole with a dose of 600 mg, and we now have another antithyroid agent which has not been used much as yet, that is 2-mercapto imidazol. We do not as yet have enough data on methylthiouracil or on aminothiazole and, certainly, almost no data as yet on 2-mercapto imidazol, as to what the incidence of complications is or what the effectiveness is. We have a large amount of data available on the complications with thiouracil and with propylthiouracil, and we are trying, in the large material we have at hand, to find out what the complication figures are with these various groups.

We have now had something over 1500 consecutive patients with hyperthyroidism, either of primary or secondary variety, and have employed all these agents in preparing this group for subtotal thyroidectomy. Most of our experience has been with thiouracil, propylthiouracil and not methylthiouracil.

We have learned that if a patient is sensitive to thiouracil we can often change to propylthiouracil, to which he may not be sensitive, and complete the reduction of the metabolism to normal, that if he is sensitive to propylthiouracil we can change to methylthiouracil and reduce the metabolism, that if he is sensitive to all three we can use aminothiazole. I wish to report a recent case in which the patient was sensitive to thiouracil, propylthiouracil, methylthiouracil and aminothiazole, in whom we were able to bring the metabolism to normal with 2-mercapto imidazol.

Doctor Bartels, who has charge of the preparation of these patients, has now received from outside sources two reports of fatalities from agranulocytosis with the use of propylthiouracil. It is important to bring this danger before the public, because there is too general an attitude that it is not possible to produce agranulocytosis of a serious nature with propylthiouracil. I would like to stress again that any agent that will reduce the metabolism is capable of depressing bone marrow in certain cases, and that precautionary

white cell counts must be done, we believe, in all cases. I believe also that I should call attention to the fact that if the white cell count drops to 4,500 and the differential to 45 per cent, it is time to stop. We know that at whatever point it stops it will still progress downward, and we prefer to stop in time rather than when the differential has been reduced to 25 per cent and the white cell count to 2,500, and then see both progress to zero.

Finally, I would like to remind you about our experience with the use of the anti-thyroid agents in children, which we have published, and in which we said that the full doses that you give adults may be given to children, and that they may be treated on the same basis as are adults.

DR JOHN H. LYONS, Washington (closing). I just want to say that the age limit at Children's Hospital is 12, which may account for the low incidence among the admissions. And I want to thank Doctor Cattell, Doctor Davison, and Doctor Lahey for their discussions.

THYROGLOSSAL CYSTS AND SINUSES*

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AND

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THYROGLOSSAL CYSTS and their associated sinuses or fistulas constitute one of the most frequent pathologic conditions encountered in the neck. In a study of patients with the various tumors, cysts and sinuses of the neck, excluding lymph-node enlargements, seen in the Lahey Clinic over a number of years, thyroglossal cysts and sinuses constituted 40 per cent of this group. We have operated on 348 patients with cysts or sinuses arising from the vestigial remnants of the thyroglossal tract, which passes from the foramen cecum at the base of the tongue to the isthmus of the thyroid gland. We have been able to follow 310 of this group of 348 patients who have been treated surgically, and this report comprises a study of these 310 cases.

The thyroid gland is developed from a median diverticulum which appears about the fourth week in embryo on the summit of the tuberculum impar, which soon after forms an invagination of the buccal epithelium just behind the tuberculum impar. This thyroid invagination passes down the neck, and its lower portion gives rise to the thyroid gland. The upper end may remain patent, it opens at the foramen cecum and is lined with pavement cells. The middle portion of the tract usually atrophies but may persist as a canal lined by columnar or ciliated epithelium, occasionally the epithelium may be squamous. The upper part of the tract, if it remains patent, forms the lingual duct, while the lower portion from the thyroid isthmus to the hyoid bone forms the thyroid duct. Toward the latter half of the second month of embryo life, the developing hyoid bone divides the thyroglossal tract into these upper and lower portions. Usually this tract atrophies and disappears at the end of the eighth week. Isolated rests of cells may persist along this tract and may give rise to a tumor which has the structure of the thyroid gland and which may present at the foramen cecum as in lingual thyroid, of which we have had three, or form cystic cavities lined with columnar epithelium and often containing thyroid follicles in the wall. Ewing¹ has stated that the thyroglossal tract, when squamous-cell epithelium is present, is a rare source of dermoid cyst. We have had several such dermoid cysts arising in the thyroglossal tract in this series. Ewing further stated that dermoid cysts in the middle of the tongue are probably derived from portions of the thyroglossal duct. Thyroglossal cysts developing in this tract may have an external opening in the neck either from spontaneous rupture or following incision and drainage of an abscess, thus forming

* Read before the Southern Surgical Association, White Sulphur Springs W. Va. December 7, 1948

a thyroglossal sinus, or may even produce a fistula if there is open communication at the foramen cecum

The thyroglossal tract is firmly adherent to the hyoid bone and it is this adherence or involvement of the hyoid bone that makes it necessary to remove the central portion of the hyoid bone to prevent recurrence of the condition. There are several theories as to the involvement of the hyoid bone. Ewing and Fraser² stated that the thyroglossal tract passes down in front of the hyoid bone but is adherent to it. Sir Arthur Keith³ believes that the hyoid bone develops in the course of, and interrupts the continuity of, the thyroglossal tract, so that the position of the thyroglossal duct may vary in relation to the hyoid bone.

A thyroglossal cyst or sinus may be found at any level in the midline of the neck from the foramen cecum to the suprasternal notch, but the majority occur

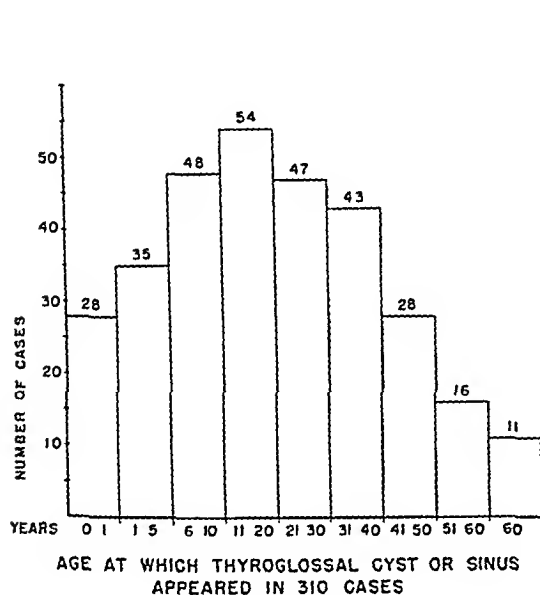


FIG 1

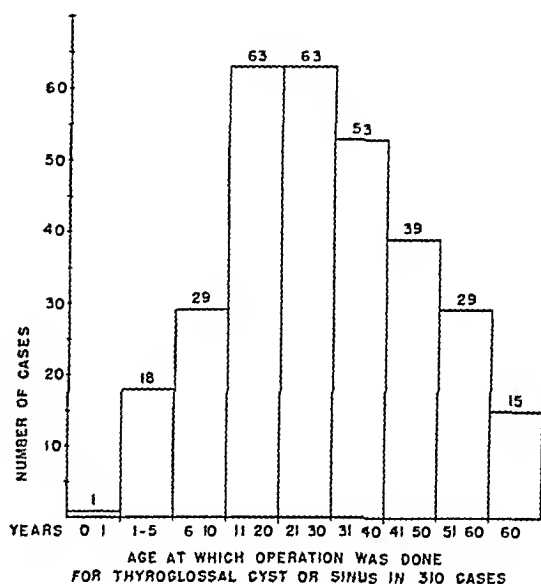


FIG 2

just below the hyoid bone. Of 310 operated cases followed, 61 occurred above the hyoid bone. It is also true that most cysts and sinuses occur in the midline, but it is well to remember also, as Bailey⁴ has emphasized, that cysts at the level of the thyroid cartilage may be situated to the left of the midline. He has pointed out that the levator glandulae thyroideae in the majority of cases is found on the left side of the cartilage and one may, therefore, expect a cyst developing at this level to be on the left side of the neck.

Thyroglossal fistula or sinus is very rarely a congenital condition. Sir John Bland-Sutton⁵ believes that they are never congenital. Bailey stated that in a review of 32 cases he found only two fistulas present at birth. In this series of 310 cases, of which 93 (30 per cent) were sinuses, we found no record of any sinus noted at birth. Most sinuses develop from spontaneous rupture or incision of an abscess resulting from inflammation arising in the cyst.

Gross and Connerly,⁶ in a report of 198 cases, stated that 15 per cent were

sinuses but did not record if any of the sinuses could be classified as strictly congenital. Gross and Connerly reported that 29 per cent of their thyroglossal cysts were present at birth and 76 per cent were noted before the sixth year, but as their study was made from material in a large children's hospital, one would expect a high percentage of these to show symptoms in early childhood. In our series of 310 operated cases, 28 patients, or 9 per cent, had cysts which were first noted in infancy (less than one year) and 111, or 37 per cent, had symptoms before the age of 10 years, in contrast to Gross' series, 68.4 per cent in this series first noted symptoms before the age of 30 (Fig 1). Our hospital admissions, on the other hand, are largely adults rather than children. Thyroglossal cysts or sinuses, as it appears from this study, may make their first appearance at any age.

Patients with thyroglossal cysts and sinuses may be seen for treatment at any age. In the largest group in this series, however, the cysts occurred before

TABLE I—Sex Distribution

	Larhey Clinic Series		Pemberton Series
	Cases	Per Cent	Per Cent
Females	173	56	33.8
Males	137	44	66.2
Total	310		

the age of 41 years (227 of 310, or 73.2 per cent, Fig 2). The patient may not come to the physician for treatment until some months or even years after, only 48 (15.5 per cent) came for treatment before the age of 10 years, whereas 56 per cent had surgical treatment before the age of 30 years. It is of interest, however, that these embryologic tracts will remain quiescent in the neck for years and then suddenly give evidence of their presence by forming a cyst, this development of fluid may be evidence of irritative phenomena, probably inflammation, which may well account for the sudden development of a cyst. That inflammatory changes do arise frequently is illustrated by the fact that approximately 50 per cent of patients give a definite history of inflammation before coming for treatment. Apparently these tracts or the epithelial cells lining them do not take on new growth or truly become neoplastic, and if this were true, one should more frequently see malignant disease developing in these tracts. We have had only one case of carcinoma developing in a thyroglossal tract in 310 operated cases.

Thyroglossal cysts or sinuses apparently are slightly more common in females than in males. In our series of 310 patients there were 173 females (56 per cent) to 137 males (44 per cent, Table I). One would expect a preponderance of females since thyroid disease is more common in women than in men. This is exactly the proportion of males and females noted in Gross' series. However, Pemberton⁷ reported a marked difference in 293 operated cases, the percentages being 66.2 males to 33.8 females (Table I).

Our oldest patient was 75 years of age and there were 15 patients over the age of 61 years. It is probably not significant that only one patient was operated on during the first year of age, as our hospital admissions rarely include infants. However, if the cyst is small and does not enlarge or is subjected to recurring inflammation, it is probably wise to postpone operation until the child is older. It is probable that most of these patients will subsequently need radical removal.

The diagnosis of thyroglossal cyst is not difficult. The presence of a firm cystic tumor in the midline of the neck at the level of the hyoid bone or over the thyroid cartilage is usually sufficient, to make the diagnosis. Transillumination is of little use as few cysts are translucent. The complication of infection or drainage in a thyroglossal cyst may be confused with tuberculous pretracheal gland but these are relatively rare today and diagnosis must be established by pathologic section. Elevation of the tumor mass by swallowing or protrusion of the tongue will help to make the diagnosis, and this sign is of value in distinguishing it from a true sequestration dermoid cyst occurring in the midline. Branchial cysts are lateral, occur under the sternohyoid muscles and usually develop later in life than do the thyroglossal cysts. Lipomas can be distinguished by the distinct edge and lobulation of the tumor, whereas the thyroglossal cyst is round and tense without edge and lobulation.

The successful treatment of thyroglossal cysts and sinuses, as Sistrunk pointed out in 1920, is the removal of every trace of the thyroglossal tract up to the foramen cecum at the base of the tongue (Fig 3). Sistrunk⁸ early realized that the majority of operations for cure were unsuccessful because this epithelial tract running from the cyst or sinus to the foramen cecum was not completely removed. Such radical removal should include the central portion of the hyoid bone. Schlange,⁹ in 1893, and Durham,¹⁰ in 1894, excised this central part of the hyoid bone and dissected the tract up to the base of the tongue, but Sistrunk¹¹ went further and advised a method that would make certain the complete excision of the tract to prevent recurrence. The cyst and part of the tract below the hyoid bone can be dissected readily up to the hyoid bone but above this level the tract is so small and tenuous that traction will easily tear it off and

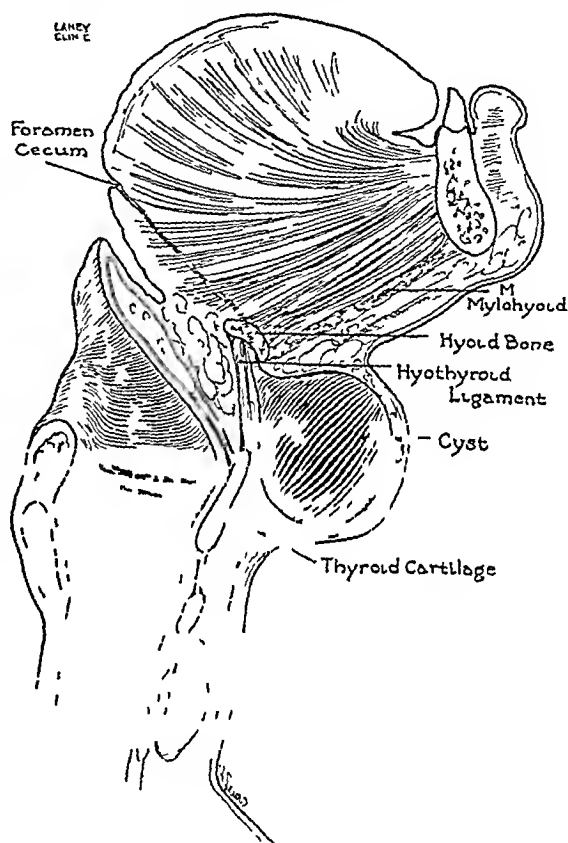


FIG 3—Sagittal section of the neck, showing the relationship of the thyroglossal cyst to the hyoid bone and the course of the thyroglossal tract above the hyoid to the foramen cecum.

identification and subsequent removal are impossible. He made no attempt to isolate or identify the tract above the hyoid bone but advocated removal of all tissues in the course of and about the duct, he stated "instead remove with duct all tissues surrounding it for $\frac{1}{8}$ inch on all sides." He suggested a "coring out of all tissue and muscle upward and backward to the foramen cecum in a line drawn at a 45 degree angle through the intersection of horizontal and perpendicular lines to the center of the hyoid bone" (Fig 4)

A transverse incision, 6 to 7 cm in length (Figs 5, 6 and 7) is made at the level of the hyoid bone or, if a sinus is present, an incision is made at the

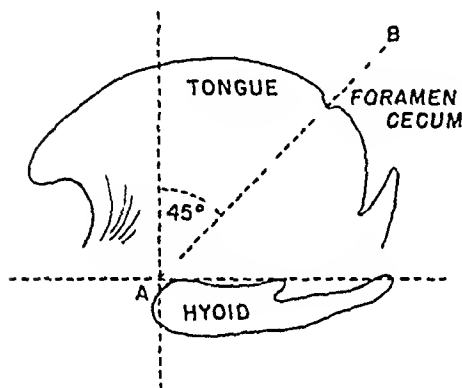


FIG 4—Sagittal section of the tongue, showing the course of the thyroglossal tract from the hyoid bone to the foramen cecum (taken from Sistrunk)

level of and about the sinus opening to permit excision of this area. When a sinus is present, its course may be outlined by injecting it with methylene blue. However, infiltration of methylene blue into the tissues after the incision is made may instead interfere seriously with following the course of the sinus. We have rarely used it and in most cases have found it to be unnecessary. The skin, subcutaneous tissue and platysma muscles are reflected, the sternohyoid muscles are separated in the midline, exposing the cyst, which is separated posteriorly from the thyrohyoid membrane up to the hyoid bone, which is cleared of muscles, and a central portion,

1 cm in length, is divided by bone forceps and elevated with the cyst (Fig 5). A "coring out of tissues" is made to include a portion of the median raphe of the thyrohyoid and a portion of the geniohyoid and genioglossus muscles up to the foramen cecum (Fig 6). The line of dissection can be made easier by placing the index finger of the left hand in the patient's mouth and pushing the patient's tongue at the foramen cecum upward and forward (Fig 8). If anesthesia is induced through a closed system by an endotracheal catheter, the anesthetist instead of the surgeon may identify the position of the foramen cecum and elevate the tongue with his index finger. The position of the anesthetist's finger can easily be identified by the surgeon through the muscles of the floor of the mouth, thus contamination is avoided and the use of the surgeon's two hands is permitted to complete the dissection more easily. As both Sistrunk and Pemberton have pointed out, we have seen no difficulty arise from removal of the central segment of the hyoid bone.

In most cases it is not necessary to carry the dissection into the mouth and the dissection can be stopped before dividing the mucosa at the foramen cecum. No harm is caused, however, by the dissection entering the mouth. The muscles are brought together with fine plain catgut and the cut ends of the hyoid bone are approximated by sutures in the muscles and tissue adherent to the bone. A small rubber tissue drain is placed between the muscles at the level of the hyoid

bone and brought out between the sternohyoid muscles and skin incision, which is approximated with sutures of fine silk (Fig 7)

Cauterizing agents and sclerosing fluids are of no value in the eradication of thyroglossal cysts and sinuses. It is difficult to see how such agents can penetrate all the epithelial-lined tracts constituting the vestigial remnants of a persistent thyroglossal duct. These agents may make later radical removal a

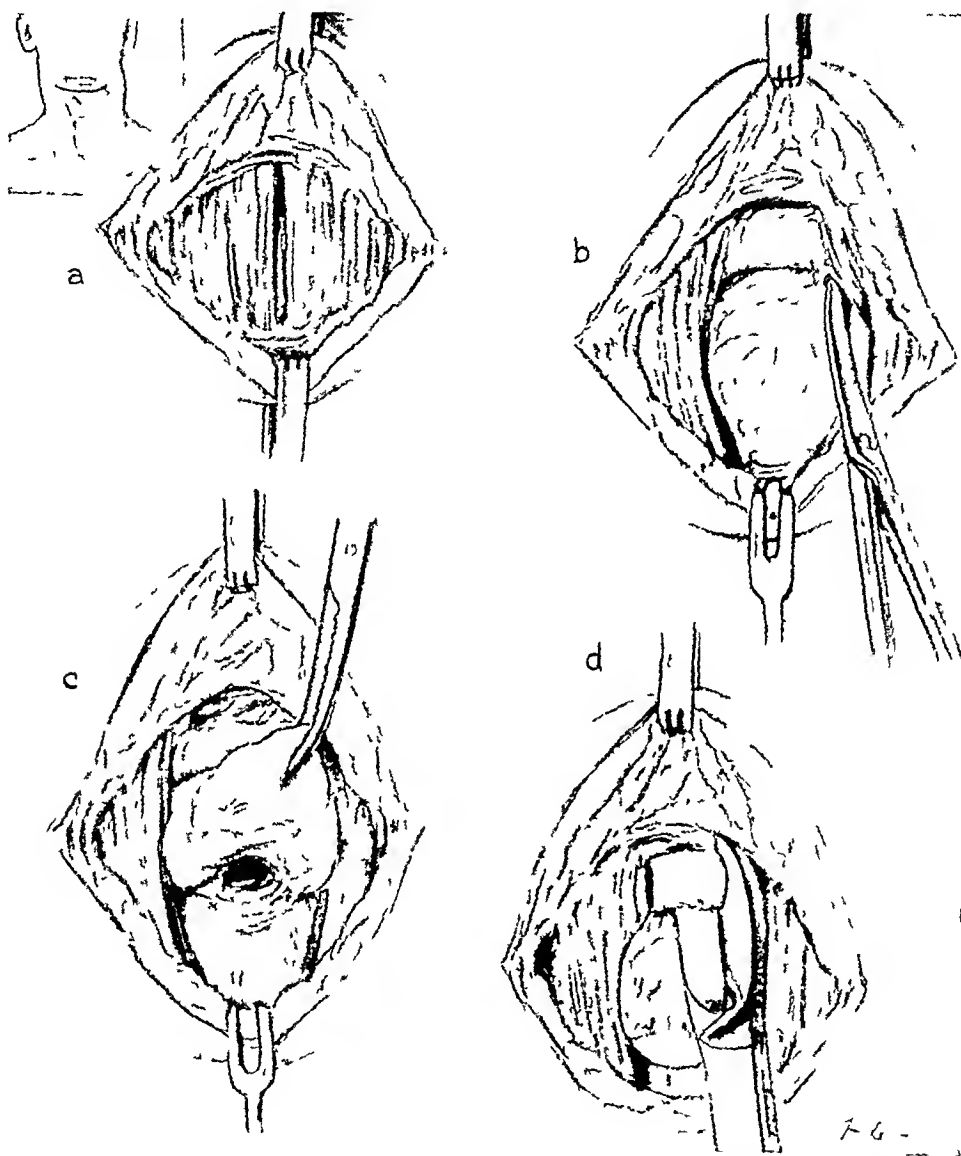


FIG 5—Operative technic (Insert) The level of incision, (a) reflection of skin, subcutaneous fat and platysma exposing sternohyoid muscles, (b) exposure of thyroglossal cyst and hyoid bone, (c) dissection of cyst from thyrohyoid membrane, (d) excision of central part of the hyoid bone

more difficult technical procedure. Many of the patients in this group of 310 cases had had previous operations with recurrence, 110 patients (35.5 per cent) had been operated on elsewhere before admission, 34 had had incision and drainage, 52 had had attempts at excision which did not include removal of part of the hyoid bone and 24 other patients had had multiple operations—

one patient had as many as six unsuccessful attempts at extirpation of the thyroglossal cyst (Table II)

Inflammation occurs frequently in thyroglossal cysts, and approximately 50 per cent of the patients gave a previous history of redness and soreness over the

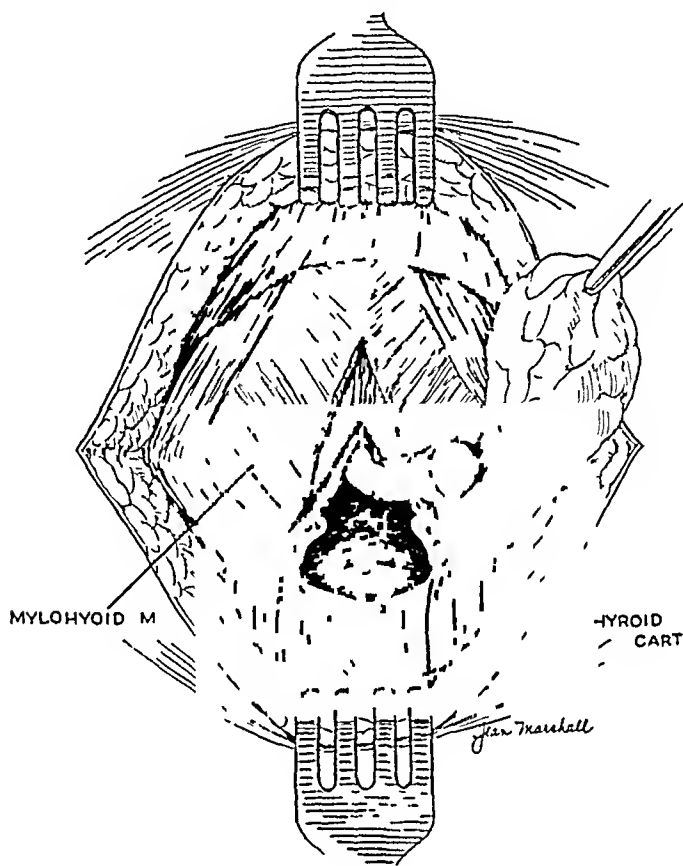


FIG 6—Operative technic Anteroposterior view of dissection of thyroglossal tract, the cyst has been dissected free from the thyroid cartilage and the thyrohyoid membrane, the central part of the hyoid bone has been excised and the tract with the core of muscles—mylohyoid, geniohyoid and genioglossus—is excised through the tongue to the foramen cecum

TABLE II—Previous Operation in 310 Patients

Incision and drainage	34
Excision	52
Multiple operations	24
	110 35.5 per cent

cyst If inflammatory reaction is marked and has progressed to suppuration, it is much safer to make an incision, drain the cyst and postpone radical removal until all inflammation has subsided In this series of 310 patients, incision and drainage was necessary in 15 cases before radical removal of the cyst and the thyroglossal tract could be carried out

With an occasional exception, the radical operation has not been made more difficult by previous surgical interference inasmuch as the previous operation has almost without exception been done without attempts at removal of the hyoid bone, so that the more difficult part of the extirpation, that is, removal of the central part of the hyoid bone and the tract above the bone, has not been interfered with. In these cases the dissection above the bone can be carried out as readily as in the primarily operated cases.

TABLE III—*Recurrence After Radical Removal*

	Cases	Recurrence	
		Cases	Per Cent
Previous operation	110	1	0.9
No previous operation	200	3	1.5
Total	310	4	1.3

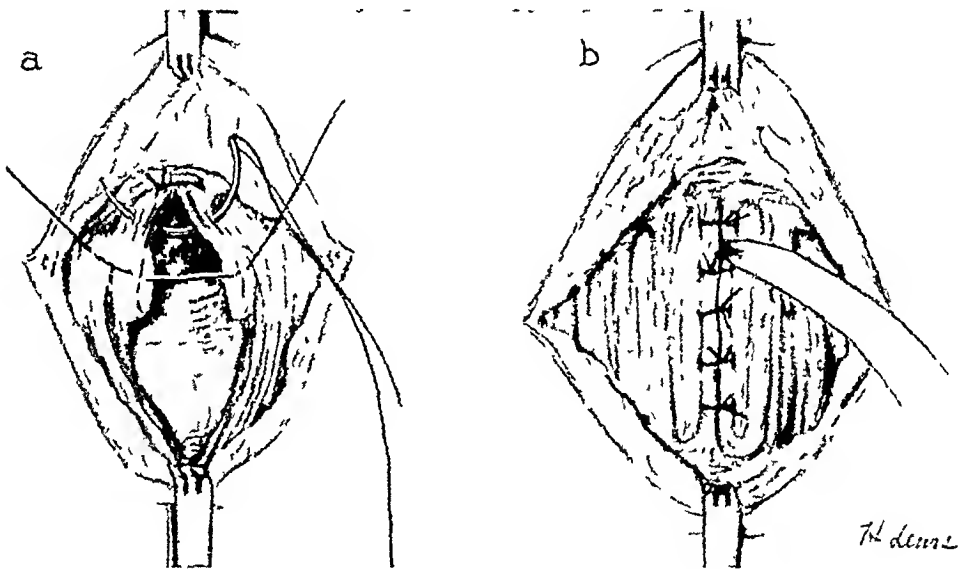


FIG 7—Operative technic (a) Approximation of the muscles of the tongue and the hyoid bone, (b) suture of sternohyoid muscles with a drain placed deep to the muscles of the tongue

In our experience, recurrences are related to nonremoval of the central portion of the hyoid bone and the tract above the bone. We have had four recurrences in 310 operations and in each instance the recurrence took place in cases in which the hyoid bone or the tract above the hyoid was not removed. We have had no recurrences when a thorough radical operation was carried out (Table III). One must emphasize the fact that radical and complete operation must be done even when involvement of the hyoid bone with the cyst or tract is not apparent to the operator if recurrences are to be avoided. We have been concerned with the problem of malignant disease developing in a thyroglossal cyst or tract. However, we have had only one such instance of an adeno-

carcinoma arising in a thyroglossal cyst which, after radical removal, has not recurred after 17 years. Malignant degeneration apparently is quite uncommon and no mention is made of it in the literature on this subject.

SUMMARY

Thyroglossal cysts, sinuses or fistulas constitute one of the most common congenital anomalies arising in the neck and occur in the midline of the neck.

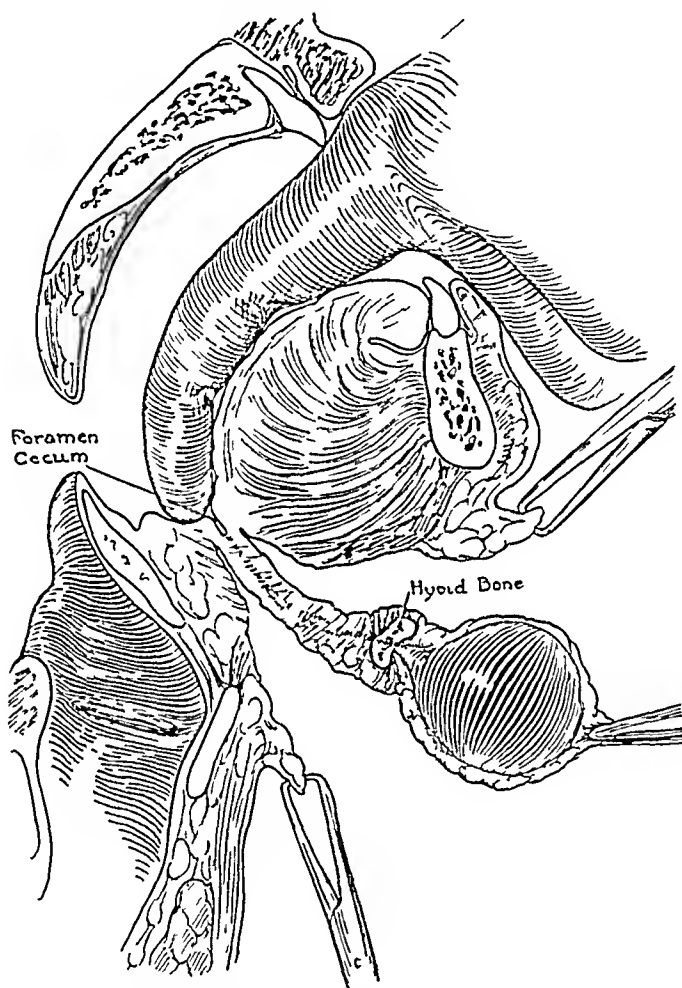


FIG 8—Sagittal section of the neck, showing the course of dissection of the thyroglossal tract, the finger in the mouth indicates the position of the foramen cecum.

at any level from the base of the tongue downward to the suprasternal notch. Cysts are found more commonly below the hyoid bone than above it.

Three hundred and forty-eight patients have been operated on in this clinic for thyroglossal ducts and sinuses. A report of their occurrence and the results obtained in 310 operated cases is given.

Successful treatment of this condition is dependent upon complete removal of the entire thyroglossal tract, which must include excision of the central part of the hyoid bone plus the tract extending above the hyoid to the foramen cecum.

There have been four recurrences following operation in 310 cases. All of these recurrences were related to nonremoval of the hyoid bone and tract above the bone.

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DISCUSSION —DR WILLIAM H. PRIOLEAU, Charleston, S. C. Needless to say, I am in thorough agreement with Doctor Marshall's able presentation of this subject. I rise only to point out one technical procedure which I have found of advantage on several occasions.

In some cases the thyroglossal duct tract extends too low to permit its satisfactory removal through the incision outlined. In such cases a second, or even a third horizontal incision placed inferiorly to the first will permit its removal in a stepladder fashion and avoid the unsightly scar from a vertical incision.

DR S. F. MARSHALL, Boston (closing). I would like to thank Doctor Prioleau for emphasizing the importance of variation of the incision, and if a sinus is present of course the incision has to be adapted to the level of the sinus, which also applies to the level of the cyst. I would like to reemphasize the great importance of removing the entire tract even in the face of no apparent adherence or involvement of the hyoid bone. If we cannot find involvement of bone or extension of the tract above the hyoid bone, it should be removed anyway because the tract may be so small that we cannot see it. Certainly the four recurrent cases that we had, have been related to this in two cases, and in the other two the fact that the tract could not be made out to involve the bone influenced the surgeon against removal of the central part of bone.

PRIMARY REPAIR OF SEVERED PAROTID DUCT

REVIEW OF LITERATURE AND REPORT OF THREE CASES*†

ROBERT S SPARKMAN, M D

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IN THE EXTENSIVE LITERATURE dealing with parotid fistula and delayed reconstruction of the severed parotid duct there are frequent references to the distressing situation of the patient who must contend with copious fistulous discharge of saliva. The notorious difficulty of successful repair of fistulae or of delayed reconstruction of the duct is attested to by the number and variety of corrective procedures which have been suggested^{7, 11, 13, 17}. In a situation in which successful primary repair seems so desirable, it is surprising that so few such repairs have been reported. There are only nine reported instances of successful repair in which any details are given as to technic or outcome.

In 1916 Schmieden¹ reported the primary suture of a severed parotid duct and stated that he had successfully undertaken a similar repair on a former occasion. Both operations were performed on the battlefield. The account is fragmentary and is not accompanied by any details of technic or information as to eventual outcome. This is thought to be the first record of an attempt at primary repair of the parotid duct.

The first detailed account of such a procedure was contributed by Tees² in 1926 in a report of two cases of successful primary repair. In each instance anastomosis was accomplished over a segment of stiff number one catgut, two fine catgut sutures were used to maintain the ends of the duct in apposition. In the first case the catgut dowel within the lumen of the duct was allowed to project into the mouth. In the second case the catgut dowel was short enough to be contained entirely within the duct, since it was felt that the catgut would undergo digestion. No follow-up was given.

The report of Tees is the only one which deals with more than a single case. Seven authors have each recorded one instance of successful repair.

Dickinson³ in 1920 used double-zero chromic catgut to suture the severed duct over a length of silkworm gut which projected into the mouth and was sutured to the oral mucosa just beyond the ostium of the duct. A gauze drain was placed in the wound. The silkworm gut inadvertently came out on the second day. An external fistula became apparent on the tenth day but closed after one month, and the patient appeared well after six months.

Black and Flagge⁴ in 1928 passed a ureteral catheter through the mouth into the two segments of the duct and approximated the severed ends with chromic zero catgut. One inch of the catheter was allowed to project intra-orally. The patient was maintained on a liquid diet for seven days and on the ninth day the catheter was removed. Subsequently a small collection of fluid

* From the Department of Surgery, Southwestern Medical College, and the Parkland City-County Hospital.

† Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 7, 1948.

was aspirated from the cheek on several occasions. At frequent intervals over a period of several weeks the duct was catheterized in the hope that stricture at the site of anastomosis might thereby be prevented. Six months after injury there was no evidence of difficulty.

In a very brief account in 1934 Hill⁵ described the repair of a severed parotid duct with three equidistant sutures of double-zero plain catgut. A laceration in the parotid gland was repaired with the same material and a small rubber drain brought out one angle of the wound. A small salivary fistula persisted for ten days. After two months the wound remained healed and saliva could be seen emerging from the ostium of the duct. The omission of any type of dowel or intraluminal fixation in this procedure is notable.

In 1935 Brohm and Bird⁶ laid emphasis upon the importance of the dowel, but stated that it should not be large enough to occlude the lumen, since the saliva could better drain around than through it. They state "The only feature that appears to offer any difficulty is the matter of fixation of the dowel." In the case reported by them the duct was anastomosed with interrupted fine silk over a filiform urethral bougie which, after emerging from the ostium of the duct, was brought out through the cheek and sutured to the skin at its point of exit. The filiform bougie was removed after seven days. Primary healing was attained. Clear flow of saliva and absence of swelling of the cheek were observed over a period of five months. The authors directed attention to a technic described by Butler and Guinan⁷ in a report of a secondary repair wherein an indwelling ureteral catheter was anchored to the canine tooth of the upper jaw. It was suggested that the small range of to-and-fro movement of the catheter attendant upon opening and closing the jaw might be advantageous.

Christofferson, Ajalet and Gradman,⁸ in 1943, anastomosed the cut ends of the duct with interrupted fine silk sutures over a single strand of horsehair, which was taped with adhesive to the angle of the mouth. The dowel was removed on the seventh day. The wound healed by first intention and salivary secretion was noted from the second day. Convalescence was uncomplicated through a period of 80 days.

In 1945 Wallace⁹ employed a technic similar to that of Dickinson,³ with anastomosis over a strand of silkworm gut which was sutured to the oral mucosa. Sutures of interrupted cotton were used to approximate the duct. The silkworm gut was removed after seven days. Two weeks after injury the wound was healed and there was no swelling of the cheek.

In 1947 Goodall and Flanders¹⁰ brought the total number of reported cases to nine in an account of successful repair of the duct over a ureteral catheter. Interrupted sutures of fine black silk were used to approximate the duct. The catheter was secured to the lower lip with tape and was left in place until the fifth day, during which the patient was allowed nothing by mouth. The wound healed without drainage and salivary secretion from the ostium was observed on the seventh day. A sialogram performed six months after injury showed the duct to be patent and disclosed no evidence of stricture. This is the only record up to that time in which sialography has been employed to establish proof of successful primary repair.

ANATOMY

The parotid duct is most liable to injury as it traverses the surface of the masseter muscle (Fig 1)

Anatomic drawings commonly show an accessory mass of parotid tissue surrounding the duct in its masseteric portion McCormack, Cauldwell and Anson¹² were able to demonstrate such masses in only 19.7 per cent of anatomic dissections (15 of 76 cases) In three specimens double ducts were noted which united within two centimeters of the anterior border of the gland

CASE REPORTS

Three cases of severed parotid duct were admitted to Parkland City-County Hospital between February 25 and July 14, 1948 Detailed case reports follow

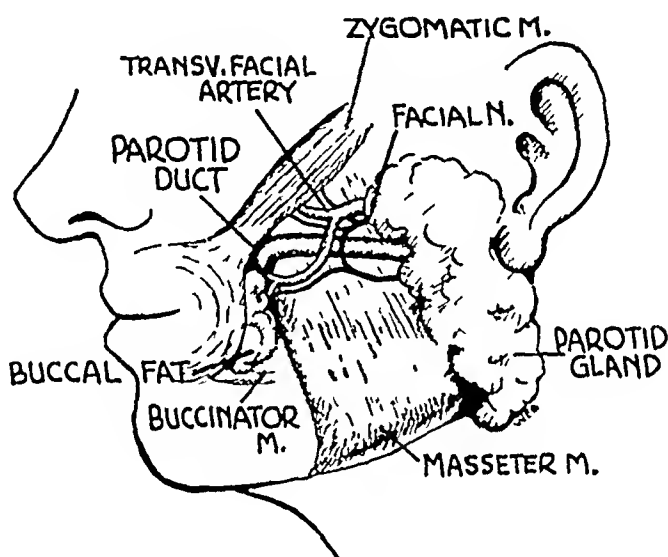


FIG 1—Anatomy of parotid duct

Case 1—L. T., male, white, age 33 On February 25, 1948, the patient was struck in the left cheek with the butt of a broken bottle and sustained an extensive irregular laceration in the shape of an inverted V. The upper angle of the wound began over the midportion of the zygoma. One vertical limb extended down to a point just lateral to the angle of the mouth, and the other to the region of the midportion of the ramus of the mandible. Most of the wound involved the entire thickness of the cheek and communicated freely with the oral cavity. There was lower facial paralysis. The wound was bleeding profusely.

Repair was begun approximately two hours after injury, and was accomplished under local infiltration anesthesia with 1 per cent procaine. Because of the loss of blood into the oral cavity, the initial step consisted of closure of the oral mucous membrane with interrupted fine cotton sutures. The wound was then subjected to thorough cleansing, and the principal source of bleeding, from the transverse facial artery, was controlled. The superficial division of the masseter muscle, which was completely severed in its tendinous portion, was repaired with mattress sutures of cotton. The distal end of the severed parotid duct was clearly exposed for two centimeters of its extent. The point of its division was approximately one centimeter anterior to the parotid gland. The proximal end was identified by its profuse discharge of saliva. A number five ureteral

PRIMARY REPAIR OF SEVERED PAROTID DUCT

catheter was threaded into the distal end of the duct and brought out into the mouth. The butt end of the catheter was then cut on a bevel and introduced into the proximal end of the duct. Anastomosis of the duct was accomplished over the catheter, employing an atraumatic suture of number six-zero eye silk. Two initial interrupted sutures were placed opposite one another in the circumference of the duct and were subsequently used as guys. Two small everting mattress sutures and four additional interrupted sutures completed the anastomosis. No sutures were allowed to penetrate the lumen of the duct. The catheter was then withdrawn from the duct through the mouth. The few fibers of the facial nerve which could be identified were so small that no attempt could be made to repair them. The wound margins were revised to accomplish the best possible cosmetic result, and the remaining layers were closed with interrupted fine cotton sutures.

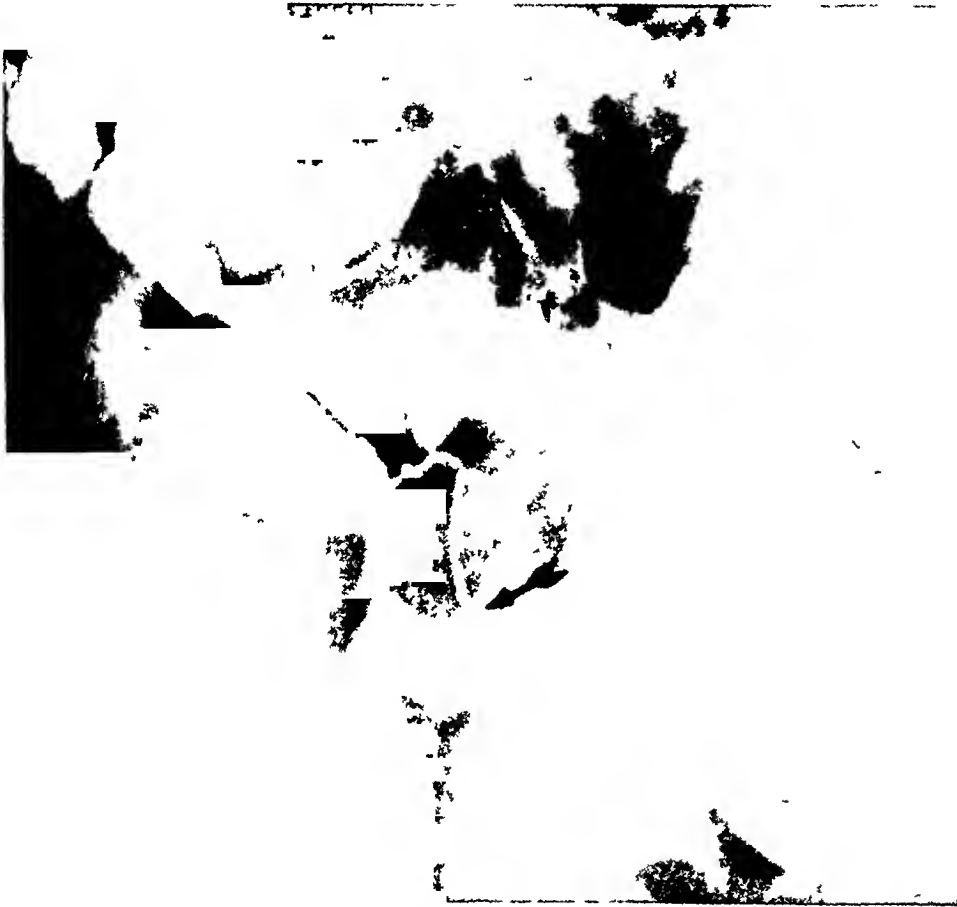


FIG 2 (Case 1)—Sialogram eight months after repair of parotid duct. Approximate site of repair is indicated by arrow. Apparent defect distally corresponds to point of passage of duct through buccinator muscle.

For a period of three days subsequent to the operation the patient was allowed only liquids by mouth. This restriction of diet was dictated by the laceration of the masseter tendon rather than by the laceration of the duct. Penicillin (50,000 units) was administered every three hours for three days. Saline mouth washes were employed at four-hour intervals. An ice bag was applied to the cheek during the first day. The initial diffuse swelling of the cheek regressed rapidly after two days. The wound underwent primary healing. The patient was dismissed from the hospital on the fourth day, by which time a flow of saliva had been observed from the ostium of the duct.

Sialograms were performed on July 14, 1948 (four months after repair) and on November 3, 1948 (eight months after repair). On each occasion the duct was demonstrated to be patent, with no evidence of stricture. There has been progressive restor-

ation of facial movement At the time of the last sialogram (Fig 2) residual facial paralysis was negligible

Case 2—F M, male, Negro, age 22 On June 4, 1948, the patient received a vertical, seven-centimeter knife wound of the left cheek situated over the midportion of the masseter muscle Lower facial paralysis was present, and there was profuse bleeding from the wound Because of the location and depth of the wound, an injury of the parotid duct was suspected Accordingly, while the patient was still in the emergency room, a number six ureteral catheter was introduced through the ostium of the left parotid duct, whereupon the tip of the catheter appeared in the wound After establishment of the diagnosis the catheter was withdrawn

Repair was undertaken three hours after injury, employing infiltration anesthesia with 1 per cent procaine Bleeding from the transverse facial artery was controlled The parotid duct was severed over the midportion of the masseter muscle, the tendinous portion of which was also partly divided Following thorough cleansing of the wound, the tendon of the masseter muscle was repaired with interrupted cotton sutures The ends of the divided duct were readily identified and were each dissected free for a distance of about five millimeters Salivary secretion was observed from the proximal end of the duct The butt end of a number four ureteral catheter was threaded into the proximal end of the duct and the tip passed through the distal end of the duct and recovered in the mouth Anastomosis of the duct was then performed over the catheter, using six interrupted sutures and two everting mattress sutures of number six-zero atraumatic eye silk (see Case 1) None of the sutures penetrated the lumen of the duct Upon completion of the anastomosis, the catheter was withdrawn through the mouth The few fibers of the facial nerve which were seen were thought to be too fine to permit repair The wound was closed in layers with interrupted fine cotton sutures

Following operation, the patient received 30,000 units of penicillin every three hours and was given mouth washes of dilute hydrogen peroxide He was placed on a regular diet within 12 hours after repair of the duct At no time was there significant swelling of the cheek The first attempt to examine the ostium of the duct was made on the third day, at which time the flow of saliva could be observed readily Primary wound healing occurred and the skin sutures were removed on the fourth day The patient was dismissed from the hospital on the fifth day On the 14th day, examination of the ostium of the duct again disclosed salivary secretion, and a sialogram demonstrated the patency of the duct This patient has subsequently left the community and has been lost to further observation

Case 3—J W, male, Negro, age 25 On July 3, 1948, the patient was admitted in mild shock His only injury consisted of a deep laceration of the left face which began just above the auricle and extended downward to a point one centimeter lateral to the angle of the mouth Satisfactory response was obtained to the administration of plasma and whole blood Repair was begun five hours after injury and was accomplished by Dr Joseph M Cox* The parotid duct was severed over the midportion of the masseter muscle The duct was repaired over a number four ureteral catheter, the end of which projected into the mouth Two everting mattress sutures of number six-zero atraumatic eye silk were placed opposite one another in the circumference of the duct The anastomosis was completed by two continuous sutures of the same material, each of which traversed one-half the circumference of the duct No sutures penetrated the lumen The catheter was withdrawn from the mouth at the conclusion of the anastomosis Two smaller ducts from which saliva was exuding were observed The distal segments of these ducts were not identified The proximal segments were ligated with cotton No attempt at repair of facial nerve fibers was undertaken The wound was closed in layers with interrupted fine cotton sutures The anesthetic agent was 1 per cent procaine by local infiltration

* Resident in Surgery, Parkland City-County Hospital, Dallas, Texas

Following operation, the patient was given saline mouth washes and 50,000 units of penicillin every three hours. He was allowed to take a general diet on the morning following operation. The wound underwent primary healing. On July 12, 1948 (ninth postoperative day) a sialogram was made and the patient was dismissed from the hospital.

He was seen again four months after injury, when sialography was repeated. At each examination salivary secretion was observed to be coming from the orifice of the duct. Beginning restoration of facial movement was apparent.

Both sialograms demonstrated patency of the duct, with questionable slight constriction at the site of anastomosis. However, the fact that the duct was not dilated proximally provides evidence that any constriction which may have existed did not constitute functional obstruction.



FIG 3 (Case 3)—Sialogram four months after repair of parotid duct
Double duct is visualized

An additional feature of interest was disclosed by sialography. A secondary duct, extending forward from a point near the anastomosis, was demonstrated running parallel to the major duct and joining it a short distance proximal to the ostium (Fig 3). This evidently corresponded to one of the proximal segments ligated at the time of operation.

DISCUSSION

In discussing the problem of primary repair of the severed parotid duct, Goodall and Flanders¹⁰ make the statement that "success of the procedure seems to have depended on the use of an inlying dowel firmly fixed in place at the time of early débridement and on the anatomic structure of the duct which makes it suitable for suture." It is probable that an additional factor is of salient importance in favoring a satisfactory restoration of continuity of the duct, to wit, the volume and pressure of the secretion of the parotid gland.

Thus, the same factors which tend to create a fistula in one situation may in more favorable circumstances tend to avert one by maintaining a large volume of flow along the lumen of the duct, even against mild degrees of obstruction. If this hypothesis is tenable, it would constitute an argument not only in favor of omission of a dowel but also for feeding the patient (as was done in these three cases), or for taking other measures to augment salivary secretion, rather than attempting to suppress it. The experience of the three cases under consideration would lead one to think that the importance of the dowel has received undue emphasis. Indeed, the partial obstruction created by some of the larger agents which have been utilized may have contributed to the development of some of the temporary fistulae which have followed attempts at repair.

Presumptive evidence of successful repair may be adduced from the following: (1) absence of swelling of the cheek, (2) absence of external drainage, (3) demonstration of salivary secretion from the orifice of the duct. It would be possible to argue that the first two circumstances could be attained either by complete occlusion of the duct (with cessation of function of the gland) or by development of an internal fistula. Moreover, the appearance of salivary secretion at the duct orifice could conceivably occur from accessory parotid tissues situated distal to the point of division of the duct. Incontrovertible evidence of the success of restoration of continuity of the duct can probably be established only by sialography.

The experience in Case No. 3 of the discovery of an accessory duct, although doubtless an extremely uncommon situation, constitutes an indication that the wound should be searched for accessory ducts or for the escape of additional saliva following repair of the major duct.

The problem of management of the associated facial nerve injury is one which merits special consideration. Seeley¹³ has stated "that while many cases of separate injury of the duct and facial nerve exist . . . it is more than likely that if parotid duct injury exists, peripheral nerve injury is also present, and vice versa. If a lacerating, penetrating, or avulsion injury involves the parotid duct, the buccal and zygomatic branches of the facial nerve will be involved." One might add that the transverse facial artery is likely to be severed as well.

Regarding the management of the associated injury to the facial nerve fibers, Seeley quotes Dr. Truman G. Blocker¹⁴ to the effect that in maxillofacial injuries in World War II the peripheral facial nerve branches nearly always regenerated spontaneously following injury at this level. Doctor Blocker¹⁵ has reaffirmed this view in a conversation with the author. Dr. James Barrett Brown,¹⁶ in a personal communication, has expressed the view that the anastomosis of fine components of the buccal and zygomatic branches of the facial nerve is not only unnecessary in this region, but is hardly possible in view of their fine caliber. He suggests the employment of a directional suture if a larger trunk presents itself, but feels that accurate layer apposition of tissue and clean healing probably favor regeneration of small nerve components as much as anything else. Definite facial weakness was suffered by the three patients here reported. No attempt was made to repair the seventh nerve com-

ponents in any of them. Facial weakness is now negligible in the patient who has been followed for eight months, and improvement in function is just becoming apparent in the patient who has been followed for four months.

There are many accounts of spontaneous healing of traumatic salivary fistulae. It is likely that spontaneous healing is more probable in injuries to the glandular substance than in those which sever the principal duct. Even where the creation of an internal fistula is feasible, the loss of the sphincter may give rise to severe ascending infection, as described by Newman and Seabrook.¹¹ In any case, the problems presented by salivary fistulae are frequently of such magnitude that successful primary repair is highly desirable. The suggested steps which may be helpful in achieving successful primary repair are as follows:

1. Anastomosis of the severed duct over a ureteral catheter, the diameter of which corresponds to the diameter of the duct.
2. Employment of multiple fine sutures which do not penetrate the duct lumen.
3. Withdrawal of the catheter at the conclusion of the anastomosis.
4. Inspection of the wound for accessory ducts which may become apparent after completion of the anastomosis.
5. The institution of a postoperative regime which favors continued secretory activity of the gland.
6. Periodic dilation is not necessary for the prevention of stricture of the duct at the site of repair.

SUMMARY

The literature dealing with primary repair of the severed parotid duct has been reviewed. To the nine cases heretofore reported three cases have been added. Three functional end-to-end anastomoses of severed ducts were performed successfully. Primary healing occurred. The patency of the repaired ducts has been demonstrated by sialography. Suggestions are made for operative and postoperative management.

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DISCUSSION —DR DRYL HART, Durham, N C I should like to present a case of reconstruction of the duct which is somewhat related to this problem. The patient had received at very close range a gunshot wound through the side of his face, so that it destroyed all soft parts in a line from the angle of the mouth to the edge of the parotid gland. He refused treatment as long as he could get his mouth open. After cicatrization pulled the teeth together so tight that he could not open his mouth he sought surgical relief. In closing the defect, we had the problem of reconstructing the parotid duct which had been destroyed. A pedicle flap lined on both sides with epithelium was raised from the chest. One of the epithelial surfaces was to line his mouth, the other to form the skin of the face. We then dissected out the scar tissue so that the mouth could be opened widely. The duct was cut off until it was free of cicatrization and was found to be somewhat dilated, due to partial obstruction. A long flap of mucosa with enough tissue to give an adequate blood supply was cut folded back to place the mucous membrane outside, and sutured in apposition with the severed end of the duct medially. No sutures were placed in the lumen of the duct, but connective tissue was sutured to connective tissue so that the epithelium of the duct and the epithelium of mucous membrane were in apposition but not sutured. We then cut the epithelium for lining the mouth in a tennis racquet shape, to fill the defect in the face and with a long prolongation to extend back to the duct. This was placed to overlie the mucous membrane strip to the duct. The connective tissues were sutured so as to keep these two epithelial strips in apposition. The closure of the defect with the remainder of the tube flap was completed. Healing was perfect.

The patient obtained full motion in the mandible but would never permit completion of the operation to give him the best cosmetic result at the angle of the mouth. We followed him for four or five years, but he refused further surgery for cosmetic results. He had no trouble with the parotid gland.

DR T G BLOCKER, JR, Galveston I think Doctor Sparkman has used very good judgment in the treatment of the three cases he has reported. We have used a similar method with stainless steel wire in anastomosing the parotid duct in a patient operated on approximately eight hours after injury. We left a drain in because of the possibility of contamination resulting from the length of time following injury. The patient developed a fistula postoperatively which, however, healed spontaneously, and except for two episodes of swelling of the parotid gland within a year, both controlled by chemotherapy, he has remained perfectly all right.

In another instance which occurred in the Texas City disaster, the parotid duct was severed near the entrance into the mouth. This was recognized at the time and treated by our usual method of handling large external fistulas of Stenson's duct. It was transplanted

into the mouth, posterior to the mucosal laceration through a triangular mucosal flap—a very small one—and by blunt dissection the duct was put into the mouth, using the apex of the flap to place in a slit on one side of the duct to prevent a stricture. This procedure worked very well in that particular instance.

With regard to facial palsy, I feel definitely that accurate approximation will allow a certain amount of regeneration of the peripheral fibers of the facial nerve. In my experience there has always remained some lag of the muscles of the affected side of the face.

DR. E. A. KITLOWSKI, Baltimore. I want to call attention to that facial lag. In our experience we have found that facial lag will be more or less noticeable depending on how much support one gives the muscles during regeneration of those nerves, and we have quite frequently used a small hook in the corner of the mouth, attached to a strap fastened to a head band which counter-pulls the muscles on the other side. In other words, we overcorrect with this apparatus, and we usually have the patient wear it during the night, in the daytime it is not so necessary because the muscle will not get sufficient damage during half the time to prevent its losing its elasticity. In that way we have been able to avoid a permanent sag in these cases and we are reasonably sure that after the nerves regenerate there will be no deformity.

DISTENTION OF THE SUBARACHNOID SPACE WITH CEREBRO-SPINAL FLUID IN INFANTS, ENLARGEMENT OF THE HEAD AND SPASTICITY, SURGICAL CORRECTION*

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IT IS THE PURPOSE of this paper to segregate from a large group of infants with increased intracranial pressure due to cerebrospinal-fluid excess, a specific group in which the clinical picture is sufficiently uniform to constitute a clinical entity, the salient features of which are (1) *Increased intracranial pressure*, manifested by slow, moderate enlargement of the head, separation of the cranial sutures, bulging and enlarging of the fontanel, and overfilling and tortuosity of the scalp veins, (2) *irritative signs*, evidenced by rigidity, twitching and convulsions, and (3) *a subarachnoid space distended with cerebrospinal fluid*, as shown by pneumo-encephalography (Figs 1 and 2)

We shall present three recent cases fulfilling the conditions described above. The similarity between these and other cases previously reported in a 1928¹ communication prompts a short review of the experimental and clinical data included in that report. That work was undertaken with the purpose of experimentally producing in dogs lesions simulating those occurring in human beings when blood was present in the cerebrospinal fluid. An attempt was made to evaluate the role of blood in the cerebrospinal fluid. For example, it was our belief that in some posttraumatic patients the signs and symptoms were due to this condition alone, rather than to the effects of concussion, brain laceration or compression. At the completion of the animal experiments, it was concluded that blood mixed with cerebrospinal fluid in young and adult dogs produced marked thickening of the meninges, resulting in neurologic disturbances. These varied from slight differences in behavior to severe convulsive seizures. Some animals were severely affected by small quantities of blood, others survived more than a year and were apparently normal.

In the second part of the earlier paper, 27 case histories were recorded. They demonstrated the varied clinical and pathologic changes in the central nervous system of human beings, following introduction of blood into the cerebrospinal fluid.

CASE REPORTS — TWENTY-YEAR FOLLOW-UP STUDY

Four of the 27 cases are reviewed here because of the similarity between them and the three cases to be reported on in this paper. Case 14 represents the common type of reaction following the introduction of blood into the

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cerebrospinal fluid during birth. The condition, in this case, failed to clear up spontaneously, but was controlled by repeated lumbar punctures. Convulsive seizures started when the child was a few days old. Nuchal rigidity was noted two weeks following birth. Generalized rigidity and failure to follow objects with the eyes were present at one month. The first lumbar puncture was done at the age of two months and 13 subsequent punctures were done over a period of four months. All symptoms disappeared. Re-examination of the child at five years of age disclosed that the circumference of the head was 50 cm, the behavior was normal, there were no convulsions. However, there were occasional episodes of momentary loss of consciousness with drawing back of the head. The recent status of the patient at age 22 shows no evidence



FIG. 1—Preoperative encephalograms, Case 1, anteroposterior and posteroanterior views, showing ventricular system within the limits of normal and excess air in parts of the subarachnoid space, indicating distention of the subarachnoid space before partial drainage.

of residues of early difficulties. The childhood development was normal, the young man served in the Merchant Marine during the war, and is happily married.

Cases 15 and 17 represent the type of patient we are now reporting, presenting the salient features listed above. They failed to clear up under lumbar-puncture drainage and a more radical procedure was undertaken. Both are now normal adults.

Case 15 presented a typical picture. Six lumbar punctures were done with only temporary improvement in the rigidity and tenseness of the fontanel. At six weeks a very small, right subtemporal decompression was done with open drainage for nine days after which the symptoms returned. On the seventy-

second day after birth, a right osteoplastic flap with drainage of the subarachnoid space was done. A low-grade meningitis was disclosed at operation. At the time of the report, the child seemed entirely normal at four years of age. She has remained normal to the present time, went through college, and was married during the past year.

Case 17 had 16 lumbar punctures over a period of nine weeks without relief. The fontanel was large, the sutures separated, the veins of the scalp dilated and the head appeared heavy. At that time, a right osteoplastic flap was turned and drainage established. The improvement was only partial and the procedure was repeated on the left side at the age of 19 weeks. From this time on, the fontanel gradually decreased in size and there was every evidence that the cerebrospinal fluid absorption was normal. The follow-up, which was continued until the present year, revealed a perfectly normal adult.



FIG. 2—Preoperative lateral view of encephalogram of Case 1, showing ventricular system within the limits of normal and excess air in parts of the subarachnoid space, indicating distention of the subarachnoid space before partial drainage.

Case 16 is included as an example of an untreated case. This child was presented for examination at the age of nine months with the diagnosis of hydrocephalus. The pneumo-encephalogram showed marked distention of the subarachnoid space, with only slight enlargement of the ventricles. Treatment was refused and the condition progressed. The child was unable to sit alone and never learned to talk. He died at 13 years of age of an acute respiratory infection, never having been out of bed since birth. This typified the course of the untreated case, in which there was a slow progression of symptoms and signs, until ultimately spontaneous re-establishment of cerebrospinal-fluid absorption occurred so that enlargement of the head ceased. In this stage the picture was one of cortical atrophy with invalidism.

CASE REPORTS, RECENT

Three cases with distended subarachnoid space are presented. This report does not include accounts of patients who have recovered after repeated lumbar punctures. The three presented are those in which repeated lumbar punctures failed and drainage was established through an osteoplastic flap.

Case 1—Examined at three months because of gradually enlarging head. Pneumo-encephalogram showed a large amount of air in the cerebral subarachnoid space, with slight increase in the size of the ventricles. Bilateral craniotomy with drainage. Recovery.

T. R.—Male. Normal birth. The child appeared mildly spastic soon after birth and the head was gradually enlarging. Head circumference, 38 cm. Chest measurement, 37 cm.



FIG 3

FIG 3—Preoperative photograph of Case 2, head circumference at four months—44 cm, fontanel enlarged and slightly bulging.



FIG 4

FIG 4—Postoperative photograph, age 15 months. Ten months postoperatively, fontanel still enlarged, head circumference 51½ cm. Fontanel closed entirely at 22 months.

Diagnostic fontanel puncture with 23-gauge needle disclosed an excess of cerebrospinal fluid over the cortex. Through this puncture wound there was very free drainage of cerebrospinal fluid for 48 hours, at which time the wound was sealed with collodion. Pneumo-encephalogram showed distention of the cerebral subarachnoid space with slight enlargement of the ventricles. Left craniotomy with drainage followed ten days later by a right craniotomy. Drainage continued for a period of 50 days. Two months later the head circumference was 42 cm and the chest measured 41.3 cm. The spasticity disappeared. The head stopped enlarging. The fontanel began to close and at the present time, at the age of 12 months, the child's development is normal physically and mentally.

Case 2—Normal birth. Early gradual enlargement of the head. Frequent lumbar punctures. Osteoplastic flap. Recovery.

D. W. D.—Female. Second child. Normal spontaneous delivery after central epi-

siotomy The child was apparently normal, but several days premature The head circumference was 30 cm with gradual enlargement to a circumference of 33.9 cm on the twentieth day The fontanel was tense and the cerebrospinal fluid was xanthochromic The diagnosis by attending physicians was "hydrocephalus" From birth, feeding was difficult There was considerable vomiting and very slow weight gain The weight on the forty-sixth day was 6 lbs 3½ oz Lumbar punctures were commenced on the twentieth day and continued at irregular intervals until the one hundred thirty-seventh day after birth, at which time they were discontinued because of gradual progression of the process A right osteoplastic flap was done The brain was tense, because of the marked distention of the subarachnoid space The tension was entirely relieved by very free drainage which followed pricking of the distended arachnoid in several places In closing the wound gutta-percha tissue drains were left in place There was very free drainage for several days following the operation This gradually diminished in amount but continued to some degree until the fiftieth day The intracranial tension, as determined by palpation of the fontanel, remained normal during the drainage period and the child's general condition improved The visible scalp veins disappeared, except on crying or straining, when they could be seen very plainly The child was two years old on March 15, 1949 The circumference of the head at this time is 53¼ cm and the chest measures 51½ cm The child is alert and entirely free from symptoms The fontanel has just recently closed (Figs 3 and 4)

Case 3—Age 3½ months Gradual enlargement of the head from birth with mild spasticity Air studies revealed dilated subarachnoid spaces Bilateral osteoplastic flaps Death

R. P. M. A 3½-months-old white male infant was seen because of an enlarging head and spasticity Resuscitation of the infant following birth was necessary for a period of five minutes The attending physician noticed slight enlargement of the head shortly after birth The child when 3½ months of age was referred to us by the pediatrician, who suspected hydrocephalus The circumference of the head was 44.5 cm and the chest was 40 cm The fontanel was slightly tense and bulging This had been noticed over a period of three weeks The sutures were not separated There was a distended vein in the left parietal region There was generalized mild spasticity and poor control of the head movements A pneumo-encephalogram showed distended subarachnoid space and a ventricular system at the upper limit of normal When the child was a little less than four months of age an osteoplastic flap was turned The arachnoid was slightly grayish and markedly distended by cerebrospinal fluid The vessels seen through the arachnoid were pulsating feebly A series of holes was made in the arachnoid membrane, with a very free flow of cerebrospinal fluid As the escape of fluid reduced the tension, the pulsation in the cortical vessels was markedly increased The wound was closed, with a gutta-percha tissue drain left in place Drainage continued for a period of 30 days, during which time the condition was partially controlled However, re-examination two months later indicated that the child's course was unsatisfactory Its fontanel remained tense part of the time and the scalp veins were dilated For this reason, a flap was done on the other side, with essentially similar findings Several hours following operation the child died in circulatory collapse Autopsy disclosed no discernible cause of death The only finding was that of a thymus weighing 35 grams In spite of this, we accept this as an operative fatality The following pathologic changes were noted Grossly, the arachnoid was thickened over the lateral surfaces, especially at the Sylvian fissure and over the base Microscopically, the leptomeninges showed edema and congestive changes with slight hyperplasia, increased vascularity and round-cell infiltration (Fig 5)

ROLE OF BLOOD IN CEREBROSPINAL FLUID

We should like to consider for a moment the question of blood in the cerebrospinal fluid of newborn infants According to the work of Roberts,²

published in 1925, 14.1 per cent of 423 consecutive deliveries showed blood in the cerebrospinal fluid. A year later Sharpe³ did lumbar punctures on 500 consecutive cases and found bloody cerebrospinal fluid in 9 per cent of the



FIG 5—Sections of meninges removed at autopsy (Top) Perivascular space, showing hyperplastic meninges, undrained side (Bottom) Perivascular space from the side which had been drained 2½ months previously

babies. Approximately half of the infants with bloody cerebrospinal fluid showed clinical signs.

The reports given above would seem to force the conclusion that blood is

found in the cerebrospinal fluid in a rather large percentage of newborn infants, and Sharpe's series further indicated that a certain number of the infants with bloody cerebrospinal fluid presented signs of meningeal irritation.

It has now been approximately 30 years since Essick⁴ injected inert particulate matter, as well as blood, into the cerebrospinal fluid to produce a marked meningeal reaction, and 20 years since we showed by animal experiments and clinical studies that these changes occurred following the introduction of blood into the cerebrospinal fluid.

We have selected four papers from the recent literature which describe meningeal changes in human beings sufficient to convince the most skeptical that blood introduced into the cerebrospinal fluid does at times produce sterile meningitis.

The paper by Strauss, Globus and Ginsburg,⁵ in which they reported on their studies of spontaneous cerebral hemorrhage, demonstrated meningeal reaction of an inflammatory nature in all their cases.

Finlayson and Penfield⁶ found 21 cases of aseptic leptomeningitis in a series of approximately 1,200 craniotomies which were performed in Penfield's clinic during the period covered by their study. One similar case followed a laminectomy. In spite of drainage through the incised dura, the incidence of aseptic meningitis was 1.6 per cent.

Hammes,⁷ in 144 fatal cases with blood in the cerebrospinal fluid found that autogenous blood in the subarachnoid space is not well tolerated by the leptomeninges in man. The meningeal reaction to the blood is evident within two hours after hemorrhage. The cellular reaction is transient, but permanent effects occur in the form of patchy fibrosis of the pia arachnoid, with obliteration of the subarachnoid space. This can be demonstrated only after the blood has been present for 10 days or longer.

Alpers and Foister⁸ studied the meningeal reaction to subarachnoid hemorrhage from all causes, with similar conclusions concerning the meningeal changes but stated that they had not found in the human adult cases the same cortical changes that were reported in the dogs and infants of our report. One may observe that cortical changes occur late. Figures 7, 8 and 13, of our previous paper, showing marked cortical changes, were taken from the brains of dogs in which blood had been injected into the cerebrospinal fluid as much as six months previously.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between this and other conditions which produce enlargement of the head in infants cannot be made without examination of the cerebrospinal fluid and pneumo-encephalography. With these aids the condition can be easily differentiated from the following:

Atresia of the sylvian aqueduct with its resulting internal hydrocephalus is excluded by the failure of air to enter the ventricles, if introduced by the spinal route. It fails to pass beyond the aqueduct if the air is introduced directly into the ventricles.

Atresia of the foramina of Luschka and Magendie with obstruction to

cerebrospinal-fluid drainage, is also distinguished by the typical pneumo-encephalographic picture

Communicating hydrocephalus, secondary to inflammatory states with blockage of the cerebral subarachnoid space at the base of the brain and in the region of the tentorium, again presents its typical pneumo-encephalographic picture, with no air in the cerebral subarachnoid spaces

Space occupying lesions as tumor, abscess and hematoma present the shifting of intracranial contents which distinguishes them from this condition. The subdural accumulations of clot or fluid will be found also on subdural puncture. Fluid obtained from subdural tap in those cases of subdural accumulations will be different from the fluid obtained on lumbar puncture. In the condition described in this paper, fluid may be obtained on subdural (really subarachnoid) tap, but it will be identical with that obtained by the lumbar-puncture route. (See recent case No. 1 above.)

Meningitides are excluded by the pleocytosis and chemical changes in the cerebrospinal fluid secondary to inflammatory states.

There are, however, several other conditions which offer difficulties in differential diagnosis. This is true probably because of the lack of universal agreement as to the definition or existence of the following: External hydrocephalus, active external hydrocephalus, Quincke's meningitis, meningitis serosa, chronic arachnoiditis and otitic hydrocephalus.

We have avoided the use of the term external hydrocephalus in our title, primarily because the mere mention of the term indicated a hopeless lesion and precipitates an extremely bad reaction on the part of physicians as well as parents. Another reason is the frequent disagreement among authors as to what constitutes external hydrocephalus. Dandy,⁹ for example, defined external hydrocephalus as a condition in which fluid accumulates in the subdural, rather than subarachnoid, space. Gardner,¹⁰ on the other hand, reported three very striking cases of fluid accumulation over the cortex under the heading of active external hydrocephalus. The pneumo-encephalograms in two of his cases show extensive accumulation of air in the subarachnoid space, with the ventricles about normal in size. Gardner's article further differentiates active external hydrocephalus in which the patients had marked increase of intracranial pressure from the accumulations in the subarachnoid space, as seen in cortical atrophy, and speaks of the latter as a passive process resulting from shrinkage of the brain.

Meningitis serosa or *Quincke's meningitis* of the later literature is also characterized by accumulation of fluid under pressure in the subarachnoid space. In this condition the fluid is never xanthochromic and can be frequently differentiated by this fact. This type of meningitis is usually associated with inflammation in the paranasal sinuses, ear or mastoid, and occurs in older age groups.

The term "meningitis serosa" appeared in the literature at a time when an effort was being made to differentiate tuberculous meningitis from other types. Quincke's¹¹ article, in 1893, approximately 60 years later, did much to clarify the concept of the condition. It is primarily a sterile meningitis, occurring in association with inflammatory lesions in adjacent infected cavities. Symonds,¹²

in 1931, under the heading of "Otitic Hydrocephalus" described a group of patients with middle-ear infections who had a clinical course similar to those with Quincke's meningitis

Cases of the condition described in this paper must be differentiated from other types of chronic arachnoiditis, in which there is no increase in the cell count of the cerebrospinal fluid. During the early part of the present century, when the interest in the diagnosis and removal of brain tumors had been thoroughly aroused, there appeared in the literature articles describing cases with increased pressure which on exploration were found not to have a tumor. These cases were designated as "pseudo-tumors," after Nonne.¹³ At operation, some thickening of the arachnoid was found, general in some cases and quite circumscribed in others, resulting in the term "arachnoiditis." Horrax¹⁴ reviewed 33 cases of posterior-fossa arachnoiditis and stated that the pathologic changes showed nonspecific thickening of the arachnoid. Bailey,¹⁵ about the same time, stated that in one of these cases the process involved the cortex and was, therefore, a meningo-encephalitis. A recent case was reported by one of us¹⁶ in which there was a posterior-fossa arachnoidal cyst two years following trauma. The patient had an internal hydrocephalus, secondary to this circumscribed arachnoiditis. Differential diagnosis can be made on the history and the pneumo-encephalogram. Age incidence will help, as arachnoiditis, general or circumscribed, rarely occurs in early infancy.

ETIOLOGY

We are of the opinion that this clinical entity is due to faulty absorption of cerebrospinal fluid. This disordered absorption is brought about by blood in the subarachnoid space. In certain cases, we believe a vicious cycle is set up because of disturbed cerebrospinal-fluid absorption-vascular dynamics which is broken only by drainage of the subarachnoid space.

The disturbed absorption is initiated by choking of the "absorption channels" with degenerating blood, fibrin, cellular debris and the variable specific meningeal reaction of the individual to a foreign body in the subarachnoid space. These factors are augmented by the altered osmotic pressure of the bloody cerebrospinal fluid. The resultant increase in intracranial pressure with the concomitant alteration of the vascular dynamics perpetuates the condition. Let us therefore consider first the osmotic and then the circulatory factors involved.

The absorption of cerebrospinal fluid is influenced by the osmotic pressure of blood in excess of the osmotic pressure of cerebrospinal fluid. Normally cerebrospinal fluid has very low protein content and, consequently, a very low osmotic pressure. However, the addition of blood to the cerebrospinal fluid greatly increases its osmotic pressure and so retards its absorption. The osmotic relationship of blood and cerebrospinal fluid has been extensively studied by Weed.¹⁷ The action of the presence of blood in the cerebrospinal fluid, as a result of brain trauma, was demonstrated in animals by Parker and Lehman.¹⁸ They were able to show a quantitative increase in cerebrospinal-fluid pressure with varying degrees of subarachnoid bleeding. They also

demonstrated that the addition of whole blood, blood serum or hemolyzed red cells caused marked elevation of cerebrospinal-fluid pressure. That the increased pressure resulted from an increase in the osmotic pressure which reduced absorption of cerebrospinal-fluid pressure, varying directly with the amount of subarachnoid bleeding, has been confirmed by Webster and Freeman¹⁹

A second important factor in the absorption of cerebrospinal fluid is the circulatory one. This involves, first, the effective hydrostatic pressure of the cerebrospinal fluid over that of the cerebral venous circulation and, second, the rate of cerebral blood flow. Systemic arterial blood pressure plays no role in cerebrospinal-fluid mechanics except when there are very wide variations in arterial pressure. It has been shown that there is a direct relationship between cerebral venous pressure and the cerebrospinal-fluid pressure (Weed,²⁰ Wolff and Forbes²¹) and that there is an inverse relationship between intracranial pressure and cerebral blood flow (Kety,²² *et al*, and Wolff and Blumgart²³). With the initial inflammatory reaction of the meninges there is dilation of the vascular bed and slowing of circulation. The slowing of cerebral blood flow is subsequently furthered by the increased cerebrospinal-fluid pressure. The pressure in the cerebral veins then becomes elevated and the hydrostatic effect of cerebrospinal-fluid pressure is then lessened. The slowing of cerebral blood flow with increased venous pressure results in further decrease in the absorption rate (Lohman²⁴) and the increased cerebrospinal-fluid pressure is accentuated.

TREATMENT

Drainage of the subarachnoid space has been the therapy in our patients. The most simple type of drainage is obtained through repeated lumbar punctures. The best guide of therapy is the tension of the fontanel. If this tension cannot be kept down, further evidence of increased intracranial pressure will appear. At that time, craniotomy, with free and maintained drainage of fluid from the subarachnoid space, is indicated. By drainage of the subarachnoid space, two corrections in this deranged situation are made. First, the increase in cerebrospinal-fluid protein is removed more rapidly than it could be by the impaired circulation, thus removing the altered osmotic relationship. Second, the vascular congestion which results from increased intracranial pressure is released as the pressure is relieved so that the disturbed vascular dynamics (slowed cerebral blood flow and altered hydrostatic effect) are removed. With more adequate circulation we believe that the body phagocytes are better able to clear out the obstructed cerebrospinal-fluid absorption channels. When this has been accomplished, absorption of cerebrospinal fluid proceeds through normal routes, and drainage to the outside ceases.

Sprong²⁵ demonstrated that the beneficial effect was not through the removal of red blood cells. He stated that blood spontaneously disappeared from the cerebrospinal fluid normally within five or six days. He found that xanthochromia was entirely absent or reduced to a faint trace in six days. His careful work established these facts in cases in which there were no meningeal symptoms, and unquestionably represented the process in a number of trau-

matic patients with bloody cerebrospinal fluid. Such is the reaction in perhaps 50 per cent of infants, those who recover spontaneously. These cases need no treatment. The need for treatment is in infants showing evidence of increasing meningeal irritation and intracranial pressure long after the blood cells have disappeared, perhaps even after xanthochromia has disappeared. In Case 2, reported above, the fluid remained xanthochromic during a period of gradual enlargement of the head, which was arrested by drainage established through an osteoplastic flap 137 days after birth.

That drainage of this cerebrospinal fluid helps, we think has been proved in many cases clinically and through pathologic studies in Case 12 of the 1928 report. This child had excessive thickening of the meninges when operated upon at the age of 27 months. The excessive drainage of cerebrospinal fluid resulted, we felt, in too great a loss of fluid, and the drains were removed. In spite of this, the drainage continued and the child died as a result of fluid loss 22 days after operation. At autopsy, the meningeal thickening, which was seen at operation, was greatly reduced on the drained side, while still persisting on the opposite side. The gross and microscopic differences are shown in Figures 24 to 29 of the 1928 report. These microscopic changes were seen in Case 3 of this paper (Fig. 2).

In Hammes' cases, although the greatest number of punctures done on any one patient was nine, and none was operated upon, he stated that the incidence of fibrosis of the meninges, in those who survived long enough to show this change, was less in those cases in which a higher number of punctures had been done.

The small number of cases not benefited by simple methods of drainage should have the subarachnoid space drained by more radical means. The temporal muscle in infants is not large enough to permit adequate drainage through it. For this reason, a more efficient procedure is to be found in turning a small osteoplastic flap. An incision is made from the coronal suture over the parietal bone in a semicircular manner toward the mastoid. After retracting the scalp and separating the dura from the bone, by inserting a dissector at the posterior edge of the anterior fontanel, the bone is divided with scissors and stripped from the dura along the coronal suture. The osteoplastic flap is then fractured in a greenstick manner along the base. A dural flap is then reflected, uncovering the distended arachnoid. Multiple small tears are made in the arachnoid over the sulci. A brain spatula is passed over the surface of the brain, facilitating gentle irrigation of the cerebral subarachnoid space with saline solution. The wound is then closed in layers with a gutta-percha drain in the posterior extremity of the incision. A loose, heavy gauze dressing is applied and drainage is allowed to saturate this bandage. All dressings are allowed to remain in place for several days. Penicillin is administered prophylactically for the duration of the drainage period. If unilateral drainage does not control the condition, the procedure is repeated on the opposite side.

DISCUSSION

While pressure is not excessive in these cases, there does exist, even in the mild cases, a slight bulging of the fontanel and moderate enlargement of the

head We are of the opinion that, in addition to restoring normal cerebrospinal fluid and vascular mechanisms, a most important effect of drainage is the protection of the brain from the effects of prolonged increased intracranial pressure Without drainage the end result, as we have seen above, is marked cortical atrophy

We do not claim anything new as a clinical entity but merely want to emphasize the possibilities of complete cure in those patients who present the appearance of an early state of hydrocephalus

Peregrine W10th,²⁶ of Chestertown, Maryland, writing in the Philadelphia Journal of 1824, described "A Case of Hydrocephalus Internus "

The subject of this case was a child of two years old In about four weeks after a severe fall on her head, she became feverish, and in a day or two after the commencement of her indisposition, her fever increased, and she had a fit of considerable violence,

Attempts were made, and repeated, to purge her by jalap, senna and castor oil, but without success Copious purging soon followed the exhibition of the croton oil, and with great relief to all symptoms The pathology of this formidable disease is still, I am inclined to think, very imperfectly understood, and the treatment, under any plan, has certainly been very generally unsuccessful Of six or eight cases which have occurred in my practice, this is the only one which terminated favourably It is very possible that I may have been mistaken in my opinion concerning the nature of this case I am, however, fortified in this opinion by that of Doctor Browne, who stands, and deserves to stand, at the head of the profession here

We quote this account because we think it represents a patient with trauma, bloody cerebrospinal fluid, meningeal reaction and distention of the subarachnoid space with recovery after a very stormy course of more than four weeks We are convinced at the present time, 124 years later, that similar cases are appearing and are perhaps not recognized

Increased intracranial pressure has always been a problem in the treatment of cerebral trauma The early authors attempted to combat it by purging, and this is still practiced today, with the addition of other measures, under the heading of dehydration These measures, we feel, are effective in conditions in which it is desirable to remove fluid from the cranial cavity, whether it be the reduction of cerebral edema or the quantity of cerebrospinal fluid These methods have been used empirically before the physiology of dehydration was worked out We now know that any substance the action of which causes a relative hemoconcentration removes fluid from the cranial cavity because of the relative increase in the osmotic pressure of the circulating blood This, in turn, reduces the intracranial pressure and increases the rate of the cerebral blood flow This has been demonstrated by Shenkin,²⁷ and others We, therefore, see that empirical use of calomel benefited these patients by alteration of the absorption-vascular dynamics

In the early days of neurosurgery surgical decompression was practiced, but it remained for Cushing²⁸ to devise a well-ordered technic of decompression through muscle structures Here again, the treatment altered the absorption-vascular dynamics by reducing intracranial pressure and allowing free drainage of cerebrospinal fluid This reversal of cerebrospinal drainage persisted until the time at which the balance between the formation and the absorption of

cerebrospinal fluid was once more restored and, with the physiologic exit for the fluid sufficient, the artificial one was not necessary

In our cases, we simply advocate a more complete drainage and a type of procedure which will permit a period of drainage sufficiently long to bring about resolution of the pathologic process, at which time external drainage ceases and the drains can be removed. In Case 12,¹ in spite of removal of the drain, the normal pathways were not capable of functioning, so that the child continued to drain until he died of fluid loss. In Case 1, of this paper, the fontanel tap had to be closed by collodion because of persistent drainage through the needle-puncture wound, indicating again the inadequacy of the normal channels of spinal-fluid absorption

SUMMARY

In this communication we attempt to point out a clinical syndrome resulting from the introduction of blood into the subarachnoid space. This clinical state is characterized by three features: (1) increased intracranial pressure, (2) evidence of meningocerebral irritation, and (3) distended subarachnoid space as demonstrated by pneumo-encephalography. We emphasize that the infant with the enlarging head should be subjected to air studies to determine if this condition is present, since the response to surgical therapy appears so promising. In substantiation of the beneficial effects of surgery, we outline a 20-year follow-up on several patients reported on by one of us¹ in 1928. We also review a case of the same condition which was not treated. In this case we show that the eventual result of the long-standing increased intracranial pressure is irreversible damage to the brain. The differential diagnosis of the condition is discussed. The etiology, we believe, is due to blockage of the absorption channels of the cerebrospinal fluid with blood, secondary meningeal hyperplasia with increased intracranial pressure. This in turn is augmented by increased osmotic pressure of the pathologic spinal fluid, which further retards normal cerebrospinal-fluid absorption. These changes produce increased intracranial pressure with reduction in effective hydrostatic pressure and slowed cerebral blood flow. The intracranial pressure is further augmented by these vascular disturbances and so the cycle perpetuates itself. Drainage of the subarachnoid space relieves the altered osmotic pressure, reduces intracranial pressure and allows vascular dynamics to return toward normal. This permits the phagocytic processes of the body to clean out the blocked absorption channels, thus reversing the cycle and allowing the patient to recover. The type of operative procedure is described in detail. A case is cited from the medical literature of 124 years ago to demonstrate that this state is not new but perhaps is not as frequently recognized as it might be.

CONCLUSIONS

1. An effort is made to segregate a clinical entity from the group of infants with enlarging heads.

2. This syndrome is characterized by the appearance of irritative signs shortly after birth, followed by signs of a moderate progressive increase in the

intracranial pressure, with distended cerebral subarachnoid space and a relatively normal ventricular system

3 This condition is produced by bloody cerebrospinal fluid

4 A 20-year follow-up of previously reported cases is recorded, and three typical cases are described

5 The pathogenesis is discussed in the light of modern theories of cerebrospinal fluid physiology

6 The treatment is outlined and is studied from both the historical and the physiologic viewpoint

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DISCUSSION—DR COBB PRICHER, Nashville It is difficult to recognize the importance of the new clinical entity that Doctor Bagley has described Doctor Bagley and Doctor Thompson have been talking about a syndrome which is concerned with the appearance of blood in the cerebrospinal fluid and its consequences This is of far-reaching importance It applies not only to newborn infants, but to every person who has a head injury, and I would like to make three points In the first place, one must differentiate this entity in infants from the ordinary hydrocephalic syndrome, which is very common and which is characterized by dilated ventricles By that point alone it may be differentiated Secondly, from the subdural hematoma picture in which one taps the fontanelle in infants and gets xanthochromic fluid, and subsequently makes the diagnosis of subdural hematoma, but it may easily be confused with one of these pictures In pneumoencephalograms, which Doctor Bagley did not have time to mention, differentiation is clear

The mechanism of the production of this picture of enlargement of the head and the pressure syndrome which results from blood in the cerebrospinal fluid, may be the result of increased osmotic pressure, may be the result of increased venous pressure which disturbs the absorption-formation balance of the cerebrospinal fluid It certainly is not cerebral edema, which our President, Doctor Lehman and his associate, Doctor Parker, some time ago proved by studying the injection of blood into the cerebrospinal fluid

The treatment, drainage, which Doctor Bagley also did not have time to discuss in detail, may accomplish several things It first evacuates fluid and permit re-establishment of the formation-absorption balance in the cerebrospinal fluid mechanism, it evacuates protein, diminishes osmotic pressure of this sub-arachnoid accumulation of fluid, it permits time, which is important, in allowing for re-establishment of normal physiologic balances Finally, the significance of this problem, this syndrome, is not confined to infants who may be mis-diagnosed as having subdural hematoma, or hydrocephalus, it is very far-reaching People who have had injuries, people who develop post-traumatic epilepsy as the result of chronic arachnoiditis which is commonly diagnosed but poorly defined, the congenital mental deficiencies resulting from birth injuries, which really may be the consequence of blood in the spinal fluid at birth, many things of that type are covered by this clinical and pathologic picture

Doctor Bagley and Doctor Thompson have delved into their own records and have reported five or eight cases which have been followed for 20 years If only we all had the patience to do that, our records would be truer and more honest

DR CHARLES BAGLEY, JR, Baltimore (closing) I have nothing further to say in closing, as time does not permit us to go into detail Most of you are familiar with the subject of blood in the cerebrospinal fluid and we hope you will be interested in reading the published paper

HYPERFUNCTIONING TUMORS OF THE ADRENAL CORTEX WITH REPORT OF EIGHT CASES*

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IN RECENT YEARS the combined efforts of internists, pediatricians, chemists (particularly the steroid chemists), physiologists and surgeons have resulted in substantial additions to knowledge of the syndromes associated with hyperfunctioning lesions of the adrenal cortex. Methods for the assay of urinary steroids have been developed which are helpful in diagnosis and in determining the results of treatment. For patients presenting clinical syndromes known to be associated with hyperfunction of the adrenal cortex, the problem of differentiating between tumor and hyperplasia has been simplified, though not entirely solved, by methods of urinary assay.^{6†} Thanks to the greater availability of some of the adrenal steroids in natural and synthetic forms, the physiologic effects of several of the hormones in this group have been elucidated by both animal and clinical studies. As a by-product of these studies, it is now possible to explain many (though not all) of the symptoms and signs presented by patients with hyperfunctioning lesions of the adrenal cortices. Metabolic studies and identification of the urinary excretory products of the adrenal steroids have further clarified the pathologic physiology of these lesions.

The purpose of the present paper is to present a group of cases of proved tumors of the adrenal cortex which exemplify some of the problems encountered in diagnosis and surgical treatment. These cases, eight in number, supplement the ten cases reported by Walters, Wilder and Kepler¹⁵ in 1934 and the seven reported by Walters and Kepler¹⁴ in 1938. At the time of these earlier reports methods for the assay of urinary steroids either were unknown or were in an early stage of development, and little was known of the physiologic effects of pure adrenal steroid hormones. It seems appropriate, therefore, to report the more recent cases now in the light of our present understanding of these problems.

SYNDROMES ASSOCIATED WITH TUMORS OF THE ADRENAL CORTEX

The earlier literature dealing with tumors of the adrenal cortex contains frequent references to "the adrenal cortical syndrome." With the closer study of more cases, it has become apparent that there is no single syndrome which is characteristic of adrenocortical hyperfunction. Rather, the clinical pictures

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 7, 1948.

† Present-day knowledge of the neutral steroids in the urine of human beings in normal and abnormal states has recently been the subject of an extensive review by Engstrom.

associated with hyperfunction of the adrenal cortex are extremely protean in nature and presumably depend on the type and quantity of steroid hormones produced, the age and sex of the patient and perhaps on other factors

Although no classification of syndromes is entirely satisfactory, the one proposed by Kenyon⁵ is an excellent one. He recognized six types of clinical syndrome, namely, (1) the adrenogenital syndrome, (2) Cushing's syndrome, (3) mixed clinical pictures including features of the first two, (4) a type characterized by single or isolated endocrine manifestations, (5) feminizing syndromes, that is, feminization of men or homologous sexual precocity in girls, and (6) tumors without endocrine manifestations. The characteristics of these syndromes have been discussed by Kepler, Sprague, Mason and Power.⁷

Inclusive as this classification is, it has been apparent for some time that in an appreciable number of the cases the clinical manifestations do not conform to any of the foregoing clinical syndromes. In such cases the clinical picture is usually mixed or incomplete and consequently defies precise classification.

Among the most spectacular of the changes produced by tumors of the adrenal cortex are those in the sexual sphere. In young boys, sexual precocity of masculine type, in combination with somatic precocity, may occur. In young girls, on the other hand, sexual precocity is likely to be heterologous or masculine in character, although homologous sexual precocity with uterine bleeding and enlargement of the breasts occasionally occurs. In adult men, sexual changes are rarely observed, because a masculinizing tumor is not likely to enhance the masculinity of a male, while feminizing tumors in adult males are excessively rare. In adult women, on the other hand, heterosexual changes are relatively common. For example, amenorrhea develops, the breasts assume a more masculine type, the clitoris hypertrophies, and alopecia of the scalp in association with hirsutism and acne of the face, extremities, chest and lower part of the abdomen may occur. The term "adrenogenital syndrome" may properly be applied in cases in which changes in the direction of increased masculinity dominate the clinical picture.

The endocrine and metabolic signs and symptoms which bear no consistent relationship to the age and sex of the patient (Table I) represent an extremely varied group of disturbances. Their most complete development occurs in Cushing's syndrome,* but they may occur in varying degree among patients who do not present the complete clinical picture described by Cushing. For example, one of the patients in the present series presented some of the features of virilization (hirsutism of the face and extremities and amenorrhea), but in addition exhibited some of the endocrine and metabolic manifestations of

* It should be pointed out that in speaking of Cushing's syndrome we are referring to the clinical picture described by Cushing and not specifically to the pathologic basis for this syndrome. In the past it has been thought that Cushing's syndrome is always associated with a basophilic tumor of the anterior pituitary. Our experience and that of others, on the contrary, has shown that this syndrome may occur in the absence of a basophilic tumor of the pituitary but is probably always associated with hyperfunction of the adrenal cortex.

Cushing's syndrome (hypertension, ecchymosis, diabetes and a hypochloremic, hypokalemic alkalosis) Other patients presenting mixed or incomplete clinical syndromes are seen not uncommonly As already indicated, these intermediate clinical pictures are most difficult to fit into a rigid classification of syndromes

HORMONES OF THE ADRENAL CORTEX

To date, 27 steroid hormones have been isolated in crystalline form from the adrenal glands of animals, and their chemical structure has been determined A considerable number of these steroids have no demonstrable physiologic activity Others have striking metabolic effects Those which have been shown to have physiologic activity fall into several principal groups (Table II) †

TABLE I—*Symptoms of Tumors of the Adrenal Cortex**

I	Nonendocrine symptoms
II	Symptoms dependent on age and sex
	Boys Homologous sexual and somatic precocity
	Girls Sexual and somatic precocity, usually heterologous Sometimes uterine bleeding and enlargement of the breasts
	Men Feminization
	Women Varying degrees of virilism
III	Symptoms independent of age and sex
	Altered habitus
	Facial and abdominal obesity
	Kyphosis
	Thin arms and legs
	Purplish striae and ecchymoses
	High color
	Hypertension
	Osteoporosis
	Diabetes
	Acne
	Polycythemia
	Hypochloremic alkalosis
	Purpuric ecchymoses
	Fatigue
	Muscular atrophy

*From E J Kepler, R G Sprague H L Mason and M H Power The Pathologic Physiology of Adrenal Cortical Tumors and Cushing's Syndrome In Recent Progress in Hormone Research, The Proceedings of the Laurentian Hormone Conference New York Academic Press, Inc Publishers 1948 2 345-389

I The predominant effects of the hormones in this group are on the metabolism of salt and water Of these, desoxycorticosterone, widely used in the form of the acetate in the treatment of Addison's disease, is the most familiar When administered in excessive doses to animals or human beings, it causes retention of sodium chloride and water and an increase of the urinary excretion of potassium Edema, hypertension and congestive heart failure may result from retention of salt and water Loss of potassium may lead to profound muscular weakness These effects may explain the symptoms of hyper-

† It is realized that the boundaries between groups are not always well defined A compound in one group may have some physiologic effects characteristic of the members of another group The grouping is based on the predominant activities of the compounds in question

tension, edema and disturbances of electrolyte metabolism observed in some cases of tumor of the adrenal cortex. The production of a diabetes insipidus-like syndrome in dogs by the administration of large doses of desoxycorticosterone acetate by Ragan, Ferrebee, Phyfe, Atchley and Loeb¹⁰ suggests that the polyuria which is present in some cases of Cushing's syndrome is perhaps attributable to excessive production of these compounds. At present there is no practical method for the assay of this type of hormone in the body fluids, however, the work of Dorfman and his colleagues² on the recognition of minute quantities of desoxycorticosterone by observing its effect on the urinary excretion of radioactive sodium is a promising lead in this regard.

TABLE II—*Active Compounds Isolated From the Adrenal Cortex**

Effect	Compound
Salt and water metabolism	Desoxycorticosterone
Carbohydrate and protein metabolism	11-Dehydro 17-hydroxycorticosterone (compound E) 11-Dehydrocorticosterone (compound A) Corticosterone (compound B) 17-Hydroxycorticosterone (compound F)
Fat metabolism (?)	11-Dehydrocorticosterone (compound A) Corticosterone (compound B)
Androgenic effect	Androstenedione 11-Hydroxy- Δ^5 -androsterone Adrenosterone 17-Hydroxyprogesterone
Estrogenic effect	Estrone
Progestational effect	Progesterone

* With modifications from E. J. Kepler, R. G. Sprague, H. L. Mason and M. H. Power: *The Pathologic Physiology of Adrenal Cortical Tumors and Cushing's Syndrome*. In: *Recent Progress in Hormone Research, The Proceedings of the Laurentian Hormone Conference*. New York: Academic Press, Inc. Publishers, 1948, 2, pp. 345-389.

2. The hormones in this group have a predominant effect on the metabolism of carbohydrate and protein. The most potent hormones of this group are 11-dehydro-17-hydroxycorticosterone (compound E of Kendall) and 17-hydroxycorticosterone (compound F of Kendall). These compounds (E and F) have been available for study in only small quantities. Among other activities they are concerned with the formation of sugar from protein precursors or with inhibiting the utilization of glucose or with both. When administered to persons who had Addison's disease and diabetes, compound E intensified the diabetes by augmenting the excretion of sugar, nitrogen and ketone bodies.¹¹ White and Dougherty¹⁶ have shown that compound E causes involution of the thymus and lymphoid tissue with liberation of gamma globulins and immune bodies. Overproduction of hormones having physiologic effects like those of compound E and compound F might explain a number of symptoms observed in cases of tumor of the adrenal cortex, which are dependent on disturbances of the metabolism of carbohydrate and protein. Among these are diabetes mellitus, negative nitrogen balance, muscular wasting, weakness, osteoporosis, thinning of the skin and ecchymosis (possibly due to weakening of

the blood vessels) The now well-known effect of the adrenal cortex on lymphoid tissue might explain the lymphopenia which is characteristic of Cushing's syndrome Practical methods are available for the estimation of some of the excretion products of hormones of this type in the urine These are the determination of glyconic corticoids by the bio-assay method of Venning and associates,¹¹ and the chemical determination of corticosteroids by the method of Lowenstein, Corcoran and Page⁹ or one of its modifications At the Mayo Clinic we are using the latter or chemical method for the determination of these corticosteroids The excretion of these substances by patients who have tumors of the adrenal cortex associated with features of Cushing's syndrome is usually increased

3 In this group are compounds such as 11-dehydrocorticosterone (compound A of Kendall) which probably influence the metabolism of fat Although some clinical and experimental evidence indicates that the adrenal cortex is involved in the metabolism of fat, this is one of the least explored aspects of the function of the adrenal cortex Obesity is one of the outstanding features of some patients who have hyperfunctioning lesions of the adrenal cortex On the contrary, patients who have Addison's disease have difficulty in gaining weight Kendall,⁴ in association with Heilman, has obtained some evidence that the administration of compound A (11-dehydrocorticosterone) to certain strains of mice results in an increase in the amount of fat, measured either as per cent of the total or the absolute amount, in the animal Kochakian⁸ was able to confirm this observation in some experiments but not in others Thorn¹² has observed a decrease in the fecal excretion of fat by patients with Addison's disease who are treated with compound A Some evidence indicates that these compounds are a part of that group of hormones the urinary excretion products of which are measured collectively as the so-called glyconic corticoids or corticosteroids

4 Compounds which have androgenic, estrogenic or progestational effects, such as adrenosterone, androstenedione, 11-hydroxy-iso-androsterone, 17-hydroxyprogesterone, estrone and progesterone, are included in this group Virilism in its several manifestations, including hirsutism, baldness, amenorrhea, florid skin, hypertrophy of the clitoris, acne, masculinization of the voice in women and alteration of the habitus in the direction of masculinity might result from production of excessive amounts of androgenic material by an adrenocortical tumor Likewise, the occurrence of sexual and somatic precocity and achondroplastic habitus in children might be similarly explained

Overproduction of estrogens and compounds which have an action like that of progesterone might explain the occasional occurrence of vaginal bleeding and sexual precocity in girls who have tumors of the adrenal cortex and the occurrence of impotence and gynecomastia in men Estrogen-producing tumors of the adrenal cortex are relatively rare, but bio-assay and chemical methods have been developed for the determination of estrogens in the urine Pregnanediol, an excretion product of progesterone and possibly also of desoxycorticosterone, can be determined chemically However, the excretion of pregnanediol in the urine does not occur solely in cases of adrenocortical

tumor, for it also occurs in some instances of adrenocortical hyperplasia and ovarian tumors, and also in pregnancy

A patient who has a hyperfunctioning lesion of the adrenal cortex associated with marked evidence of virilization is likely to excrete a large amount of 17-ketosteroids in the urine. On the contrary, if evidence of virilization is minimal or lacking, as in Cushing's syndrome, the excretion of 17-ketosteroids may not be elevated

OTHER AIDS TO DIAGNOSIS

Several diagnostic procedures have been employed to demonstrate the presence of a tumor in a given adrenal gland. Occasionally, a plain roentgenogram of the renal region will reveal a soft-tissue shadow above one of the kidneys. At other times, intravenous urography will indicate a downward displacement of one kidney or urographic evidence of deformity caused by pressure from above the kidney. Obviously a tumor must be of considerable size to permit roentgenographic recognition. Unfortunately, few functioning tumors of the adrenal cortex are of this size. In our experience many of the tumors have been so small (2 to 5 cm. in diameter) that they neither depress the kidney nor lend themselves to reliable roentgenologic visualization after perirenal injection of air. Moreover, in a few cases in which we injected air, the reaction was rather shocking both to the patient and to us, so that we abandoned this method of diagnosis, not because of this alone, but also because of the ease, safety and accuracy with which the adrenal glands can be exposed through a small surgical incision.

PREOPERATIVE PREPARATION AND POSTOPERATIVE CARE

Removal of a hyperfunctioning adrenocortical tumor is an extremely hazardous procedure, as shown by high mortality rates reported in the literature, if the possibility of postoperative adrenocortical insufficiency is not appreciated. Atrophy of the contralateral adrenal cortex may be responsible for disastrous consequences if appropriate treatment for adrenal insufficiency is not administered before the operation and for several days after excision of the tumor. Proper preoperative and postoperative treatment and appropriate surgical procedures will lessen the risk. Important signs suggestive of adrenal insufficiency in the first 48 hours after operation are prostration, hypotension, tachycardia and unusual fever.

Although it has been said that acute postoperative adrenal insufficiency is more likely to occur in cases of Cushing's syndrome than in cases of adrenogenital syndrome, it has been our practice to treat all patients who have a tumor of the adrenal cortex as if adrenal insufficiency might follow removal of the tumor. Since potent extracts of the adrenal cortex have been available, no postoperative deaths have occurred in our own experience.

The most important feature of the preoperative treatment is the intramuscular administration of from 20 to 50 cc of adrenocortical extract the evening before the operation and the intravenous administration of another dose of the same size in 1 liter of physiologic saline solution on the morning of the operation. Immediately after excision of the tumor, an additional 50 cc

of adrenocortical extract is administered intravenously. For several days after the operation, from 50 to 100 cc of the extract is given daily, the dose is gradually decreased before its use is discontinued. If the patient is a child, smaller amounts of extract and fluid are employed. Occasionally desoxycorticosterone acetate in doses of from 5 to 10 mg is administered intramuscularly the morning of the operation.

SURGICAL EXPOSURE AND OTHER CONSIDERATIONS

The decision concerning which adrenal gland should be exposed first is extremely pertinent if a functioning tumor is suspected. Under these circumstances it is currently considered unnecessary to expose both adrenal glands if a tumor is found on the first side explored. We have not yet encountered a case of bilateral hyperfunctioning neoplasm of the adrenal cortex. If the location of the tumor can be determined in advance of operation, only the side in which the tumor is present need be exposed. Ordinarily the opposite gland has undergone atrophy from disuse.

The approach which one of us (W. W.) most frequently uses consists of a posterolumbar incision like that employed for operations on the kidney. The patient lies on the opposite side. Advantages of this approach are that good visualization of each gland is possible and the exposure is adequate to deal with whatever type of lesion is encountered. Bilateral incisions are made whenever necessary.

Probably the most important consideration from the surgical viewpoint is the procedure to follow after the adrenal glands are exposed. In the event that a tumor is encountered, there is little question about the procedure. The tumor should be removed in its entirety. Usually this can be accomplished. In our opinion it is ordinarily advisable to remove the involved gland completely since most of the tumors are malignant.

Treatment of the patient who has Cushing's syndrome associated with bilateral hyperplasia of the adrenal cortex is still in the phase of clinical development. Currently and for the last several years we have been employing a procedure which seems to be the most satisfactory that has been developed to date but which still leaves much to be desired. In brief, this procedure consists of exposing both glands at the time of operation to exclude the presence of a tumor. If none is present, subtotal adrenalectomy is performed on one side. From two-thirds to three-fourths of this gland is removed. Occasionally after this procedure the patient undergoes a temporary remission of symptoms for perhaps a matter of months. Subsequently, if symptoms persist or recur, about three months or less after the initial operation both glands are exposed again. The gland on which the subtotal adrenalectomy was performed is exposed first to determine that the remaining portion is still viable. If it is viable, the entire gland or three-fourths of it on the opposite side is removed. Obviously such a procedure involves exposure of both adrenal glands twice, which hardly seems ideal. Unfortunately, however, it is hazardous to remove too much adrenal tissue at any given operation, and therefore this complicated procedure is necessary.

Results following removal of hyperfunctioning tumors of the adrenal cortex are good in general and are excellent if the lesion is benign. Results following operation in cases of adrenal hyperplasia are less satisfactory. Experience with this lesion is still rather limited and it is hoped that the prognosis in cases of this condition may be improved in the future.

REPORT OF EIGHT CASES

Case 1—The patient was a man 62 years of age. Three years before his admission to the clinic in 1939, a tumor had been found in the left upper quadrant of the abdomen. This tumor had been considered to be an enlargement of the spleen. The patient had had yellow fever in 1878 and malaria in 1903 but he did not believe that the tumor had developed then. During the three years before his admission he noted progressive enlargement of the mass. Physical examination elsewhere in 1937 revealed, in addition to the

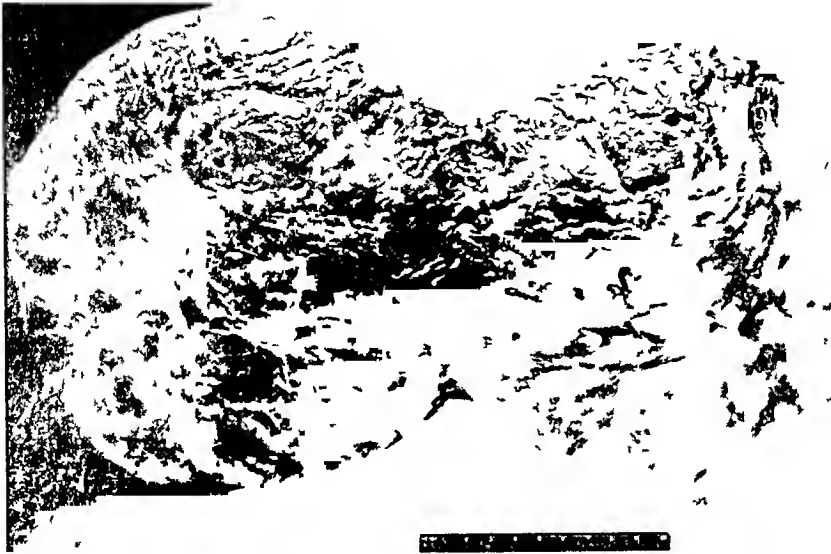


FIG 1 (Case 1)—Carcinoma of the left adrenal cortex weighing 2,685 Gm

tumor, a marked systolic murmur in the hypogastric region. The patient had been able to work daily and had no other complaints. He came to the clinic on the advice of his doctor because of the increasing size of the tumor.

On physical examination at the clinic a large, somewhat fixed mass was noted in the left upper quadrant of the abdomen, this extended to the midline and down to the umbilicus. It was globular and no notch could be felt in it. The patient presented no signs or symptoms indicative of an endocrine disturbance. The blood pressure was 112 mm of mercury systolic and 70 diastolic. Laboratory data were not significant. The value for hemoglobin was 13.8 Gm per 100 cc of blood, there were 3,970,000 erythrocytes and 6,600 leukocytes per cubic millimeter of blood. The differential count showed 22 per cent lymphocytes, 70 per cent neutrophils, 6 per cent monocytes, 15 per cent eosinophils and 0.5 per cent basophils. Examination of the blood smear showed nothing diagnostic. No increase in regeneration was noted. Serologic tests were negative for syphilis. Roentgenograms showed displacement of the stomach to the right by a large tumor. A roentgenogram of the abdomen showed a large soft-tissue shadow on the left with multiple areas of calcification throughout. The renal shadow could not be differentiated from this mass. The patient was seen by several consultants and the site of origin of the tumor could not be ascertained definitely.

On January 9, 1939, a large carcinoma of the left adrenal gland was removed (Fig 1). It was almost the size of a football, and weighed 2,685 Gm. It was surrounded by a nest of blood vessels, the pedicle of the tumor being composed of diffuse venous sinuses which were about 1 cm in diameter. The kidney appeared to be normal and was not removed. Bleeding from the blood vessels supplying the tumor was controlled by ligature. Two curved hemostats were allowed to remain for 72 hours on two veins high in the renal fossa close to the diaphragm. The pathologist made a diagnosis of primary adenocarcinoma, grade 3 (Broders' classification), of the adrenal cortex. The patient was given 300 cc of acacia, 500 cc of citiated blood, and 1,000 cc of saline solution while he was on the operating table. During the first 36 hours following the operation, there was a rise in temperature and pulse rate and a fall in blood pressure to 80 mm of mercury systolic and 60 diastolic. On the day of operation, after the origin of the tumor from the adrenal cortex had been established, and on seven succeeding days, the patient was treated with cortical extract (Kendall) and physiologic saline solution intravenously to prevent the occurrence of acute adrenal insufficiency (Table III).

TABLE III—*Treatment After Removal of Tumor of the Adrenal Cortex in Case 1*

Day	Cortical Extract (Kendall) cc	Whole Blood cc	Physiologic Saline Solution cc	5 Per Cent Solution of Glucose cc
1	20	500	3 000	500
2	50		1 000*	1 000
3†	70		2 000	
* This solution also contained 0.5 per cent sodium citrate				
† For the succeeding five days the patient received physiologic saline solution and adrenal cortex extract in decreasing amounts				

The patient's convalescence was uneventful except for the symptoms of adrenocortical insufficiency already mentioned and some separation of the wound. In order to hasten healing a secondary closure was made of it on February 2, 1939. The patient was dismissed from the clinic on March 4, 1939, at which time the wound was practically healed.

Follow-up studies were made during the succeeding seven years by physicians in the patient's home locality and on December 20, 1946, the patient, in sending a report of his progress, stated that he had been well except for pyelitis in 1945 and resection of the prostate gland in 1946. His general health at the time of writing was good, and he was working regularly. In February, 1949, the patient reported by letter that he was in good health at the age of 72 years, except for an inguinal hernia.

Case 2—The patient, a woman 27 years old, presented herself at the clinic on July 5, 1941. She complained of failure to menstruate, excessive growth of body hair and headaches associated with visual disturbance. Menses had begun at the age of 11 or 12 years. In 1939, when she was 25 years old, menstruation ceased. Following the administration of theelin twice weekly for one month, she had a little spotting of blood from the uterus. She also noted a decrease in the size of her breasts. For the two years before her admission to the hospital, there had been an increasingly excessive growth of hair over the body, especially over the legs, thigh, upper lip, thorax and abdomen. In 1935 she had begun to have visual disturbances, during which she could see the right side of an object but not the left side. Such episodes occurred once every two or three months. They were associated with headaches over the left eye. There was no visual disturbance between these episodes. The last episode had occurred two or three weeks before her entrance into the clinic.

On physical examination at the clinic the patient was found to be moderately obese.

Excessive hair was noted on the face, extremities, chest and abdomen, with a male distribution of hair in the suprapubic region (Fig 2). A mass was palpable in the left upper quadrant of the abdomen. Blood pressure was 118 mm of mercury systolic and 68 diastolic. Examination of the ocular fundi and of the visual fields disclosed no abnormalities. Routine examination of the urine and blood, determinations of blood urea, plasma chlorides and carbon-dioxide combining power and roentgenograms of the thorax, head and thoracic vertebrae disclosed no significant abnormalities. An excretory urogram revealed displacement of the left kidney downward. The urinary excretion of 17-ketosteroids was 724 mg in three days, or an average of 241 mg per day. The test for urinary prolan was negative for normal amounts. The urine excreted in 24 hours was positive for 13 rat units of estrin. A glucose-tolerance test revealed a diabetic type of curve.

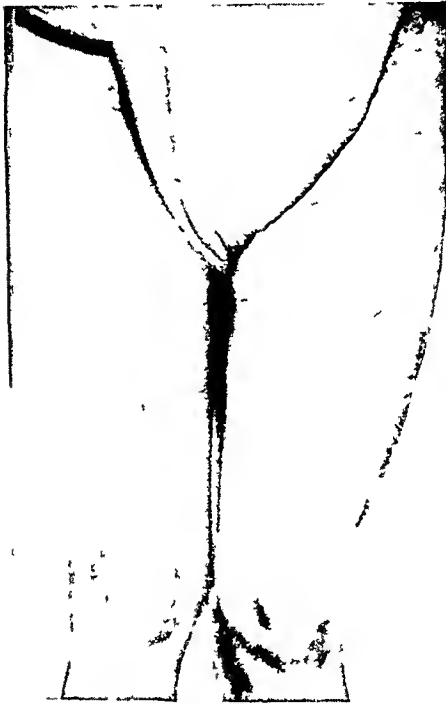


FIG 2 (Case 2) —Hirsutism of thighs

A diagnosis of tumor of the left adrenal cortex was made. The headaches were thought to be due to migraine. Preparation for operation was begun on July 14, 1941. On this day the patient twice received 10 mg of desoxycorticosterone acetate subcutaneously. On the day of operation, July 15, she was given 200 cc of physiologic saline solution intravenously and two injections of 10 mg each of desoxycorticosterone acetate.

At operation a left adrenal tumor measuring approximately 25 cm in diameter was found. The tumor was well encapsulated but was adherent to the peritoneum at its upper margin. A slight tear was made in the capsule of the tumor as it was being separated from the peritoneum. All tumorous tissue was removed and the blood vessels going into the tumor were doubly ligated. In the perirenal fatty capsule there were many large veins similar to those often seen in association with hypernephromas. The pathologist reported that the tumor was necrotic carcinoma, grade 2, of the adrenal cortex (Fig 3). On the second and third postoperative days the patient was given 5 mg of desoxycorticosterone acetate

subcutaneously and on the fourth, fifth and sixth days, 2 mg.

The postoperative course was uncomplicated except for variable fever from 99° to 101° F daily for seven days. There were no evidences of adrenocortical insufficiency. The patient became afebrile on the tenth day and was dismissed from the hospital on the 14th day and from the clinic one month after operation.

The values for urinary hormones before operation should be compared with the values after operation. There was a sharp reduction in excretion of 17-ketosteroids in the urine to 21 mg in ten days (average 2.1 mg per day) shortly after operation. Four months after the operation the urinary excretion of 17-ketosteroids was 10.3 mg in 24 hours and 11 months after operation the value was 8.6 mg.

The patient was re-examined in September, 1943. Normal menstruation had been resumed a few weeks after removal of the adrenocortical tumor. There was no evidence of recurrence of the tumor. Aside from obesity, examination revealed no significant abnormality. The body hair was entirely within normal limits. The urinary excretion of 17-ketosteroids was 7.0 mg in 24 hours.

A written report from the patient in 1947 indicated that she was in good health except for headaches.

Case 3—The patient, a girl aged 45 months, was presented for examination on March 26, 1942. The parents stated that pubic hair had been present in increasing amounts for four months and for the past month an enlargement of the abdomen had been noted. A diagnosis of an adrenal tumor had been made elsewhere.

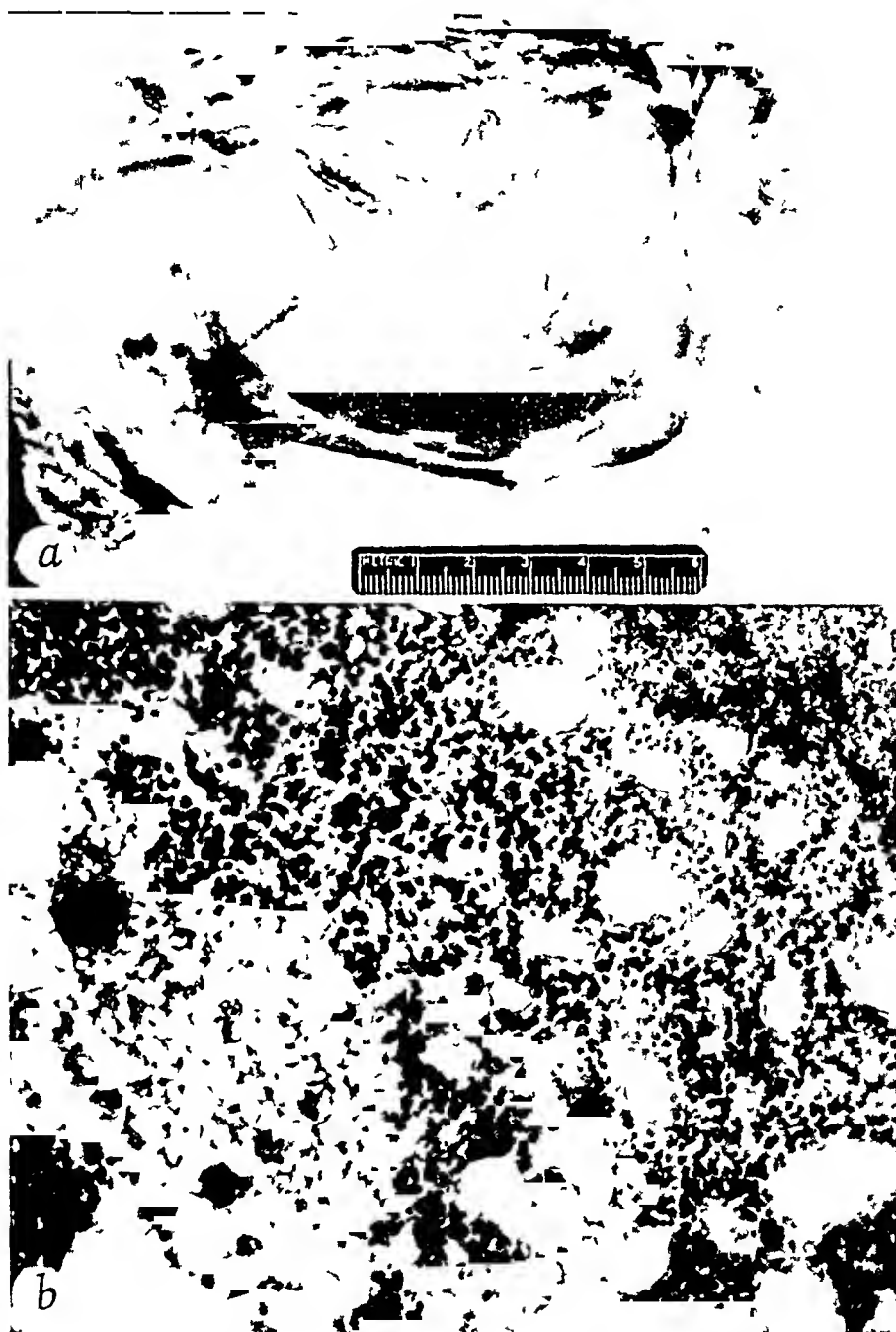


FIG 3 (Case 2) —(a) and (b) Necrotic carcinoma, grade 2, of the left adrenal cortex.

Physical examination at the clinic revealed a child with a full face, acne, red cheeks and a suggestion of cyanosis (Fig 4). The blood pressure was 110 mm of mercury systolic and 80 diastolic. Facial acne and a protuberant abdomen with a firm, fixed, nontender mass in the right upper quadrant were noted. Pubic hair was present and the vulva and clitoris were hypertrophied (Fig 5). The voice was deep for a child. Routine urinalysis showed nothing abnormal. The value for hemoglobin was 14.8 Gm. The ery-

throcyte count was 5,660,000 and the leukocyte count 9,400. The differential count was normal. Roentgenograms of the thorax and abdomen showed no abnormality, those of the bones of the wrist revealed seven ossification centers which constituted evidence of



FIG 4 (Case 3)₁—Acne and rounded contour of the face



FIG 5 (Case 3)₂—Pubic hair and enlarged clitoris

precocious development. The urinary excretion of 17-ketosteroids was 170 mg in 24 hours. The test for estrin excreted in the urine in 24 hours was positive for 16 rat units. These values should be compared with those obtained on the second postoperative day when less than 1 mg of 17-ketosteroids was excreted in 24 hours.

The child was prepared for operation by being given 5 mg of desoxycorticosterone acetate on the day preceding the operation, and on the morning of surgery she received an additional 5 mg. During the operation and subsequently that day she received 1,000 cc of 5 per cent solution of glucose in physiologic saline solution with 5 mg of sodium citrate and 30 cc of cortical extract added. Later 10 mg of desoxycorticosterone acetate was given subcutaneously. She received 500 cc of blood during the operation.

At operation, a right posterolumbar incision was made and a tumor the size of a grapefruit arising from the right adrenal gland was exposed and removed. It was attached to the peritoneum and liver. Bleeding from several large veins was controlled with hemostats. A pack was used to control bleeding from the liver. Three curved hemostats were left on the blood vessels. The child's condition was not good during the latter part of the operation, but the blood pressure stabilized later after the supportive measures previously mentioned were carried out. The pathologist reported that the right adrenal gland was 13 cm in diameter and weighed 460 Gm. There was a semi-encapsulated, hemorrhagic, degenerating adenocarcinoma, grade 3⁺, of the adrenal cortex (Fig 6).

The preoperative and postoperative treatment aimed at the prevention of adrenocortical insufficiency is summarized in Table IV. On the 11th postoperative day the patient was given 200 cc of blood and the pack was removed from the incision without any bleeding. Aside from a slight wound infection, convalescence was not complicated. No symptoms suggestive of adrenocortical insufficiency were observed.

Two weeks after the operation the value for 17-ketosteroids was 69 mg in 24 hours, this finding suggested that tumor tissue still remained.

HYPERFUNCTIONING TUMORS OF THE ADRENAL CORTEX

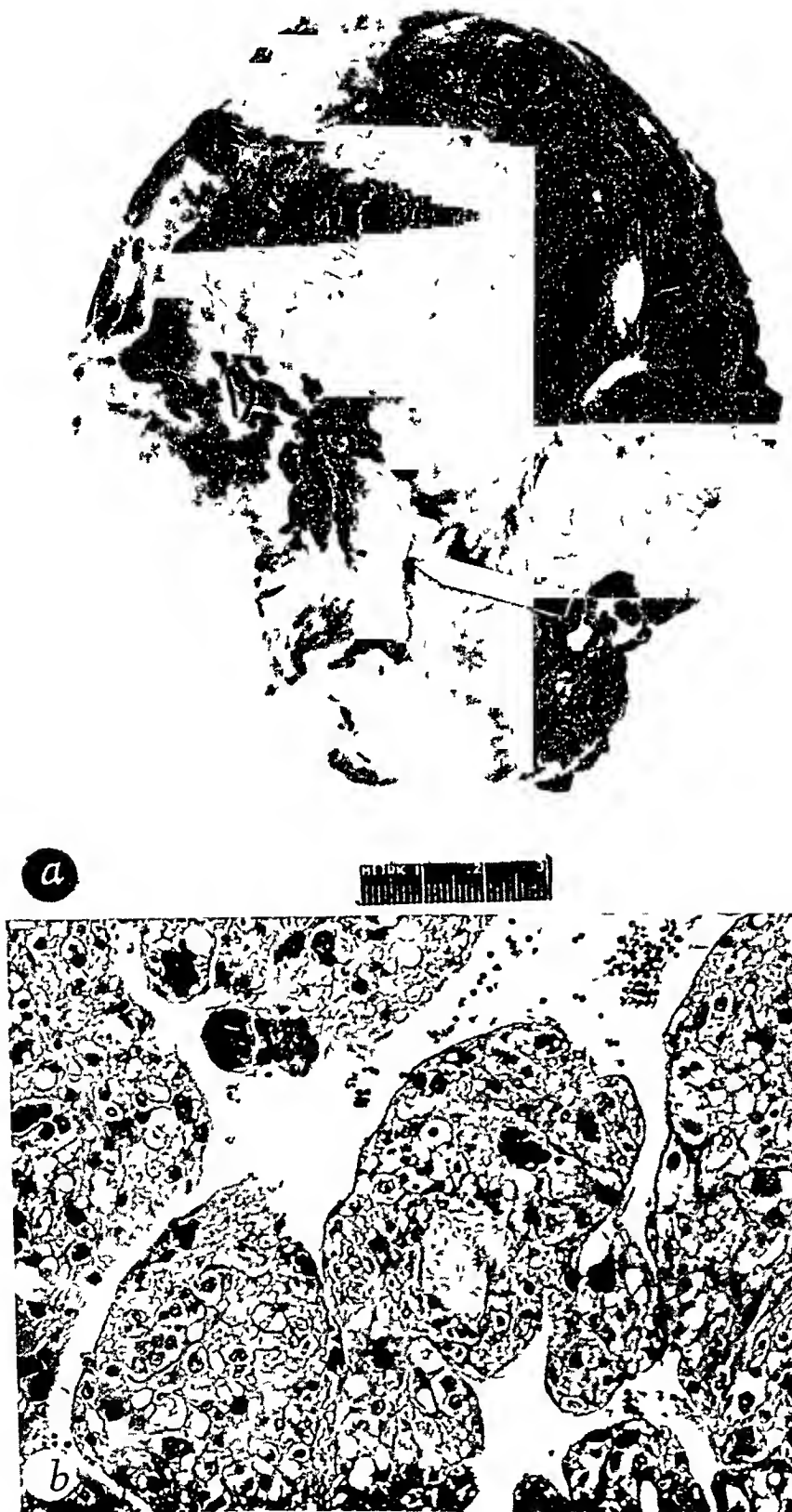


FIG 6 (Case 3) —(a) and (b) Semi-encapsulated, hemorrhagic, degenerating adenocarcinoma, grade 3⁺, of the right adrenal cortex

Three months later, the mother stated in a letter that the child was in good health. One month later the mother wrote that the child was not in good health and she was brought back for further examination. At this admission complaint was of pain in right upper quadrant of the abdomen, an increased appetite and a rash on the forehead. There was an increase in intake and output of fluids.

Examination revealed enlargement of the liver, which extended almost to the pelvis, and pubic hair. A roentgenogram of the thorax showed multiple metastatic lesions in the lungs. The diagnosis was recurrent or persistent carcinoma of the adrenal cortex, with metastasis. The course was progressively downhill and the patient died on September 18, 1942. No postmortem examination was performed.

TABLE IV—*Treatment Before and After Removal of Tumor of the Adrenal Cortex in Case 3*

Day	Desoxycorti- costerone Acetate mg	Cortical Extract (Kendall) cc	Whole Blood cc	5 Per Cent Glucose in Physiologic Saline Solution cc
Preoperative				
1	5			
0	5			
Postoperative				
1	10	30	500*	1,000†‡
2	10	40		1,000†
3	2.5			
4		20		1,000†
5		10		
6		10		
7		10		
8‡		5**		

* Given during operation

† Also contained 0.5 per cent sodium citrate

‡ Infusion begun during operation

** The patient received 2.5 cc cortical extract daily intramuscularly for the succeeding five days

Case 4—The patient, a woman 24 years of age, was first seen at the clinic on December 21, 1947. She had been married twice and had one child by her first husband. A year and a half before her admission, during the first four months after her second marriage, she had gained 37 pounds (16.8 Kg). Nine months before her admission, acne had developed on her face, arms and shoulders, and she had noted flushing of the face and facial hirsutism. Six months before her admission, progressive weakness forced her to stop work. After her basal metabolic rate was found to be -23 per cent, she was treated with desiccated thyroid and she lost 14 pounds (6.4 Kg) in four weeks. Dryness of the skin and polyuria developed. She continued to menstruate regularly but the amount was decreased.

On examination, the systolic blood pressure was 124 mm of mercury and the diastolic was 80. The face was rounded and of high color. Facial acne was present. The skin was dry. Keratosis pilaris and characteristic purplish striae limited to the flanks were noted. An excess amount of thin, blond hair was present on the face, arms and legs. The arms and legs were thin, and she had such profound muscular weakness that she could not step up on a chair. The abdomen was protuberant. The hair was "messy" and unkempt in appearance. The clinical picture was that of Cushing's syndrome of severe degree (Fig. 7).

The urine was alkaline in reaction. Polyuria was marked, the daily volume of urine ranged between 3,700 and 8,400 cc. Hemoglobin measured 16.8 Gm per 100 cc of blood. Erythrocytes numbered 4,620,000 and leukocytes 13,900 per cubic millimeter of blood. The differential count showed only 11 per cent lymphocytes. The sedimentation rate was 7 mm at the end of one hour by the Westergren method. Roentgenograms of the thorax, skull, kidneys, ureters and bladder gave no evidence of abnormality. There was no osteoporosis.



FIG 7 (Case 4) — (a) Approximately three years before the manifestations of Cushing's syndrome developed, (b) at the height of the disease, and (c) six months after removal of the tumor of left adrenal cortex.

TABLE V — *Treatment After Removal of Tumor of the Adrenal Cortex in Case 4*

Day	Cortical Extract (Kendall) cc	Physiologic Saline Solution cc	5 Per Cent Glucose in Physiologic Saline Solution, cc	5 Per Cent Solution of Glucose, cc
1	70*	1 000*		2 000
2	20		1 000	1 000
5	40		1,000	
6	40		1 000	
7	40			1 000

* 40 cc of the cortical extract and the 1,000 cc of physiologic saline solution were given intravenously during operation. This was begun immediately after excision of tumor.

The values for blood urea, serum sodium, serum potassium, serum chlorides, carbon-dioxide combining power of plasma, serum albumin and serum globulin were normal. The hematocrit reading was 56 per cent cells. On one occasion no estrin was demonstrable in the urine, and on another the test was positive for 60 rat units in urine excreted in 24 hours. The urinary prolactin was strongly positive for 5 rat units per liter. The urinary excretion of 17-ketosteroids was 7.3 mg in 24 hours on one occasion, and 3.5 mg on another. The urinary excretion of corticosteroids was 110.1 mg in 24 hours. A glucose-tolerance test revealed a diabetic type of curve.

On January 16, 1948, the left adrenal gland was exposed through a posterolumbar incision and a small, ovoid, yellow-brown encapsulated tumor involving from 65 to 75 per cent of the gland was seen. The tumor was removed and a fringe of normal gland

was left. The pathologist reported that the tumor weighed 10.5 Gm and was an encapsulated, well-circumscribed cortical carcinoma of low grade 1 (Fig 8).

The treatment with cortical extract (Kendall) and fluids which were administered intravenously after removal of the tumor is summarized in Table V. On the third postoperative day no treatment was administered, and on the fourth day the temperature and pulse rose. On the fifth postoperative day treatment with cortical extract and solutions

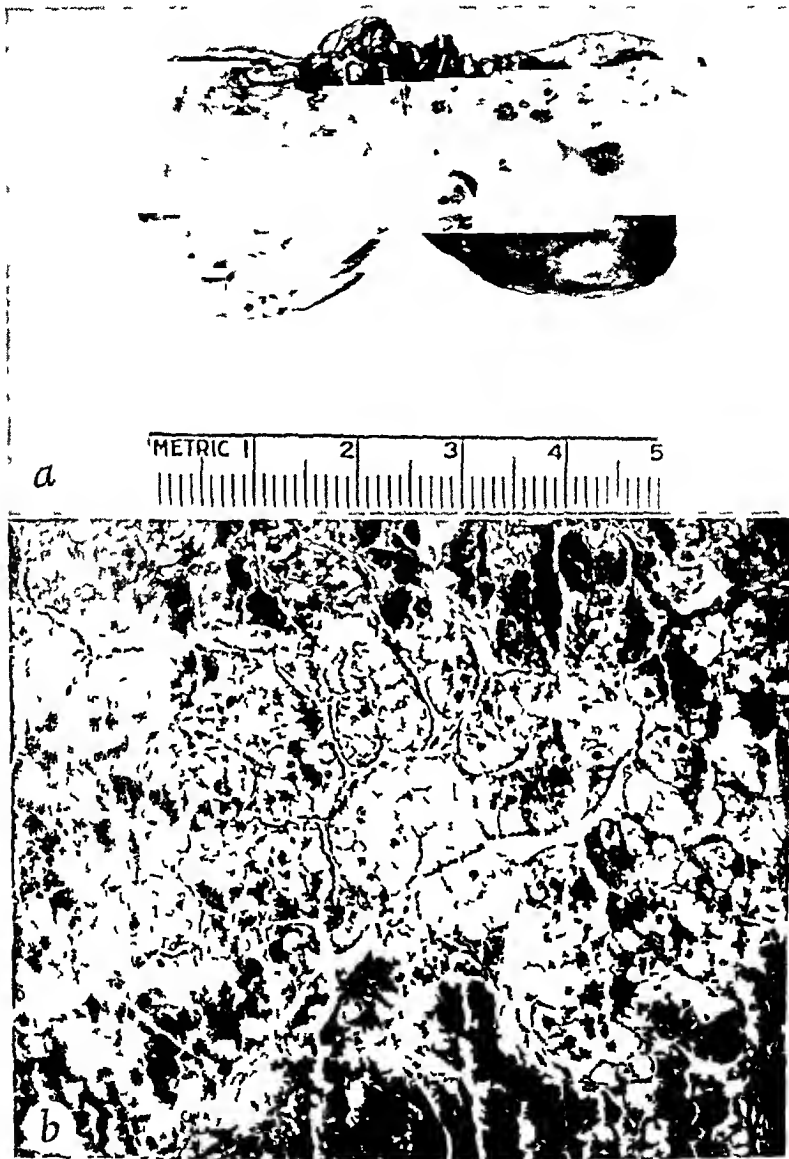


FIG 8 (Case 4) —(a) and (b) Encapsulated carcinoma, low grade I, of the left adrenal cortex

of sodium chloride and glucose was resumed. The temperature and pulse returned to normal.

During a period of four weeks following excision of the tumor of the adrenal cortex, successive determinations of the excretion of 17-ketosteroids per 24 hours, gave the following results: 2.9 mg, 1.0 mg, 0.7 mg and 1.1 mg. The urinary excretion of corticosteroids three weeks after the operation was 0.563 mg in 24 hours.

The postoperative course was marked by a troublesome cough for a few days and weakness, nausea and anorexia. The latter symptoms were still present at the time of her dismissal from the clinic on February 18, 1948.

On June 30, 1948, the patient returned for re-examination. A remarkable change had taken place in her appearance. She had become a beautiful young woman (Fig 7c). The hirsutism previously noted was gone, the skin had cleared, the striae had faded, and menses had returned to normal. She stated that her general health was good except for some weakness and occasional vomiting. Both had improved slightly when she took salt tablets. The urinary excretion of 17-ketosteroids was 16 mg in 24 hours. The differential count showed 35 per cent lymphocytes. In October, 1948, when last heard from, the patient was gaining strength and improving generally.

TABLE VI—*Treatment Before and After Removal of Tumor of the Adrenal Cortex in Case 5*

Day	Cortical Extract (Kendall) cc	Physiologic Saline Solution cc	5 Per Cent Glucose in Physiologic Saline Solution cc	5 Per Cent Solution of Glucose cc
Preoperative				
0	10	500		
Postoperative				
1	22.5*	800*		
2	15			750
3	20		1,000†	
4	10			
5	10‡			
* 7.5 cc of the cortical extract and 300 cc of physiologic saline solution were given intravenously during operation.				
† Also contained 0.5 per cent sodium citrate.				
‡ Administration of cortical extract was decreased gradually after the fifth postoperative day and was stopped on the thirteenth day.				

Case 5—The patient, a male child 15 months of age, was first seen at the clinic on April 17, 1942. For three months a marked change of physical features had been noticed. The child had gained 3 pounds (1.4 Kg). The face had become obese and hair had appeared on the face, body and genitalia. There had been an enlargement of the penis.

Physical examination at the clinic revealed an obese infant with hirsutism involving the face, thorax, back and pubic area, facial acne, a well-developed penis and descended testes. He weighed 26 pounds (11.8 Kg) and was 28 inches (71.1 cm) tall (Fig 9a). The blood pressure was 110 mm of mercury systolic and 70 diastolic.

Laboratory studies revealed alkaline urine, and 16.6 Gm of hemoglobin per 100 cc of blood. Erythrocytes numbered 4,810,000 and the leukocytes 19,600. The differential count was normal; there were 41 per cent lymphocytes. Roentgenograms of the thorax and skull revealed nothing abnormal. Roentgenologic studies of the bones revealed only conditions compatible with the patient's age. The urinary excretion of 17-ketosteroids was 41 mg in 24 hours. This may be compared with a postoperative excretion of 0.2 mg in 24 hours.

On the morning of the operation the patient was given subcutaneously 500 cc of saline solution to which had been added 10 cc of cortical extract (Kendall). On May 1, 1942, the left adrenal gland was explored through a posterolumbar incision and found to be smaller than normal. The incision was closed and a similar incision was made on the right side. An ovoid and globular encapsulated tumor was removed from the adrenal gland on this side. The specimen measured 6 by 5 by 2.5 cm and weighed 40 Gm. Microscopic examination revealed a cortical adenocarcinoma of low grade 2.

The preoperative and postoperative treatment employed in this case for the prevention of adrenocortical insufficiency is summarized in Table VI.

The patient was dismissed on the 21st postoperative day after responding to the treatment outlined. The wound had healed after slight drainage and the patient's general condition was good.

On February 8, 1943, the child returned to the clinic. His appearance had returned to normal (Fig 9b) and he seemed to be in excellent health. He weighed $27\frac{3}{4}$ pounds (12.5 Kg) and was $33\frac{3}{4}$ inches (85.7 cm) tall. The urinary excretion of 17-ketosteroids

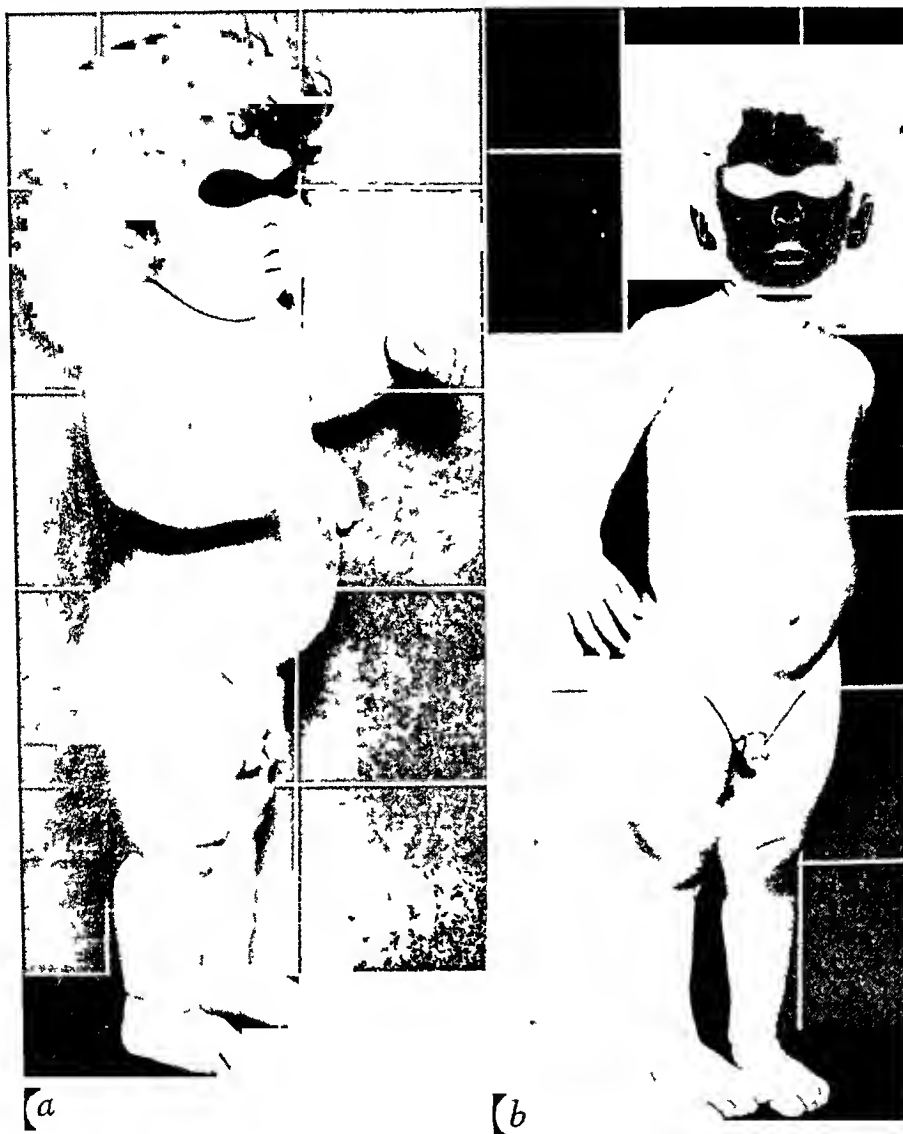


FIG 9 (Case 5) —(a) Before, and (b) nine months after, removal of the tumor of the right adrenal cortex

was 0.2 mg in 24 hours. In August, 1943, correspondence with the family revealed that the child was apparently well except for some intermittent slight drainage from a small part in the wound. In March, 1949, a letter from the child's father stated that all evidence of the trouble due to the adrenal cortical tumor had disappeared. The boy, at the age of eight years, appeared to be growing and developing normally.

Case 6—The patient, a woman 42 years old, was seen at the clinic on February 19, 1948. For two years she had had an increasingly severe lumbar backache and occipital headaches, and she had gained 20 pounds (9.1 Kg). For the year and a half before her

admission she had been bedridden part of the time because of the severe backache and headaches. She fatigued easily and lost the 20 pounds which she had previously gained. Polydipsia and polyuria had developed. Six months before her admission she noticed an increased growth of hair on the upper lip. The hair had become darker and there was hair on the cheeks and face. The facial features had thickened, the voice coarsened and menses had ceased.

On physical examination the patient was 4 feet 10½ inches (148.6 cm) in height and weighed 107 pounds (48.5 Kg). The blood pressure was 202 mm of mercury systolic and 132 diastolic. Hirsutism of the face and extremities and a dry coarse skin were present (Fig 10). Ecchymosis was present at the site of venipuncture. There was tenderness in the right upper quadrant and the right costovertebral angle. No mass could be felt. The legs were so weak that she had difficulty in stepping up on the examining table. The clinical picture was a mixed one, including features of both Cushing's syndrome and the adrenogenital syndrome.

Roentgenograms of the thorax and skull revealed no abnormality. Those of the lumbar portion of the spinal column showed slight hypertrophic changes. The urine contained albumin, grade 2, and 1 to 8 erythrocytes, and 3 to 20 pus cells per high-power field. There were 13.7 Gm of hemoglobin per 100 cc of blood, and 4,440,000 erythrocytes and 10,700 leukocytes (16.5 per cent lymphocytes) per cubic millimeter. The sedimentation rate by the Westergren method was 66 mm at the end of one hour. The value for serum potassium was 2.1 mEq, for serum chlorides, 8.9 mEq and for serum sodium 142 mEq per liter. The concentration of blood urea was 14 mg and of sugar 100 mg per 100 cc of blood. A glucose-tolerance test showed a diabetic type of curve. The excretory urogram showed a soft-tissue mass, 5 by 6 cm, adjacent to the superior pole of the right kidney and displacing it downward. Before operation 3.2 mg of 17-ketosteroids, 30 rat units of estrin and 1.04 mg of corticosteroids were excreted per 24 hours, and more than five rat units of prolactin were present per liter of urine. These values may be compared to a postoperative measurement of 0.5 and later 2.1 mg of 17-ketosteroids, 15 rat units of estrin and 0.438 mg of corticosteroids excreted in 24 hours, together with less than five rat units of prolactin per liter of urine.

On February 28, 1948, through a right posterolumbar incision, an adrenal tumor was exposed. The 12th rib was resected for better exposure and a small opening was inadvertently made in the pleura, which was immediately sutured. The tumor and all of the right adrenal gland were removed. After operation 350 cc of air were aspirated from the right pleural cavity, which resulted in complete expansion of the lung as indicated by the roentgenogram.

The pathologist reported that the tumor was 8 cm in diameter and weighed 100 Gm. On microscopic examination it was found to be a cortical adenocarcinoma, grade 3. The



FIG 10 (Case 6) —Before removal of the adenocarcinoma of the right adrenal cortex. This patient presented a mixed clinical picture, including features of the adrenogenital syndrome and Cushing's syndrome.

capsule was not intact, and because of this it was felt that the ultimate prognosis was probably poor

Before the operation and for several days after it, the patient received treatment for the prevention of adrenocortical insufficiency following excision of the tumor. This is summarized in Table VII. It is to be noted that potassium chloride was incorporated in the fluid given intravenously because of the finding of a low level of serum potassium before the operation. Recovery was uneventful except for slight anorexia on the eighth postoperative day and slight drainage from the wound. There was some anemia after operation, for which ferrous sulfate was prescribed.

In May, 1948, the patient wrote that her condition was good, that the excess hair was disappearing, and that her face now appeared normal. In September, 1948, a letter from

TABLE VII—*Treatment Before and After Removal of the Tumor of the Adrenal Cortex in Case 6*

Day P O	Cortical Extract (Kendall) cc	5 Per Cent Glucose in Physiologic Saline Solution cc.
0	50	1 000
1	60	2 000*
2	30	1 000†
3	60	2 000†

* 1.5 Gm. of potassium chloride was added to each liter of fluid because of the low preoperative level of serum potassium.

† 2.0 Gm. of potassium chloride was added to each liter of fluid.

her sister revealed the patient to be in critical condition and not expected to live. It was thought that her condition was due to recurrence of the tumor of the adrenal cortex.

Case 7—The patient, a divorced woman age 50 years, came to the clinic on July 12, 1948. She had undergone hysterectomy and oophorectomy in 1944. One year before her admission to the hospital, hypertension was found on a routine examination elsewhere. At that time she had noted fullness of the face and neck. Her friends commented on how "fat" she was, although she had not gained weight. Six months before her admission she was given phenobarbital and injections of testosterone. Red spots developed on her right arm, which persisted after this treatment was stopped. Three months before her admission a heightened color and roundness of her face had become quite conspicuous and she began to tire more easily.

Physical examination at the clinic showed her face to be round and high-colored, with fine light hirsutism. The blood pressure was 170 mm. of mercury systolic and 100 diastolic, and the body weight was 128 pounds (58.1 Kg.). The skin on the extremities was thin, and several ecchymotic areas were present. The extremities were thin, and there was a cervicothoracic hump. The clinical picture was that of Cushing's syndrome.

The urine was acid in reaction. The blood contained 13.0 Gm. of hemoglobin per 100 cc. and 4,160,000 erythrocytes and 11,400 leukocytes (21 per cent lymphocytes) per cubic millimeter. The sedimentation rate was 27 mm. in one hour by the Westergren method. The basal metabolic rate was -13 per cent. The concentration of blood urea was 28 mg., of serum chlorides 101 mEq. per liter, of sodium 149 mEq. per liter, of serum potassium 4.2 mEq. per liter and of sugar 95 mg. per 100 cc. The carbon-dioxide combining power of the plasma was 29.1 mEq. per liter. Roentgenograms showed diffuse osteoporosis of the skull with a normal sella turcica, slight osteoporosis of the entire spinal column and nothing abnormal in the thorax. An excretory urogram revealed essentially normal conditions. The amount of 17-ketosteroids excreted in the urine was 4.9 and

67 mg in 24 hours on two determinations. No estrin was demonstrated in the urine. More than five rat units of prolan were found per liter of urine, and 159 mg of corticosteroids was excreted in 24 hours. These amounts may be compared with the postoperative findings of 0.9 and later 0.7 mg of 17-ketosteroids, and 0.25 mg of corticosteroids excreted in 24 hours.

The patient was given 20 cc of cortical extract (Kendall) intramuscularly on August 29 and operation was performed on August 30, 1948. The left adrenal gland was exposed through a posterolumbar incision. No adrenal tumor was found. The wound was closed and a similar one was made on the right. An adenoma 2.5 cm in diameter was found in the lower pole of the right adrenal gland and removed. The pathologist reported the tissue removed from the right adrenal gland weighed 7.25 Gm and microscopic examination showed a hyperplastic adenoma.

Treatment before and after removal of the tumor is outlined in Table VIII. The patient exhibited no symptoms which could be ascribed with certainty to adrenocortical insufficiency, and the early postoperative course was uneventful. On the eighth day after

TABLE VIII—Treatment Before and After Removal of Tumor of the Adrenal Cortex in Case 7

Day	Cortical Extract (Kendall) cc	5 Per Cent Glucose in Physiologic Saline Solution cc	5 Per Cent Solution of Glucose cc
Preoperative			
1	20		
0	40	1 000	
Postoperative			
1	110	1,000	1 000
2	80	1 000	2 000
3	20	1 000	
4	30		
5	20		
6	10		

operation, however, she began to experience nausea, anorexia and lassitude*. These symptoms were still present when she was permitted to return to her home on September 16, 1948, 18 days after operation.

The patient returned for re-examination on January 3, 1949. Nausea and anorexia had persisted at home until the latter part of November, 1948, and her weight had declined to 105 pounds (47.6 Kg). By about the middle of November all the features of Cushing's syndrome had disappeared. With the subsidence of these features she had begun to experience aching pain and stiffness in the fingers, elbows, shoulders, knees and feet. These symptoms were present when she returned for re-examination.

Examination disclosed nothing to suggest that the patient had ever had Cushing's syndrome. The blood pressure was 115 mm of mercury systolic and 72 diastolic. She weighed 113 pounds (51.3 Kg). It was felt that the clinical picture with respect to the joints was probably that of periarticular fibrositis, but the elevation of the sedimentation rate of erythrocytes to 40 mm in one hour by the Westergren method suggested that the condition might be early rheumatoid arthritis. The urinary excretion of 17-ketosteroids was 1.6 mg in 24 hours, while the corticosteroids measured 0.35 mg. The leukocytes, 39.5 per cent of which were lymphocytes, numbered 7,300 per cubic millimeter of blood. A glucose-tolerance test revealed a normal blood-sugar curve. Roentgenograms

* This type of postoperative reaction as it was observed in four patients following subtotal adrenalectomy for Cushing's syndrome has been described in detail by Kepler, Sprague, Mason and Power.⁷

of the skull showed much less osteoporosis than had been evident in the roentgenograms made in July, 1947. Roentgenograms of the right hand showed soft-tissue swelling of the proximal interphalangeal joints, with minimal destructive changes consistent with rheumatoid arthritis.

Case 8—The patient, a girl 40 months of age, was seen at the clinic on September 9, 1947. When she was two years of age her mother had noticed enlargement of the child's clitoris. At the age of 35 months pubic hair was noted. Since the age of 32 months her habitus and face had been plumper than previously.

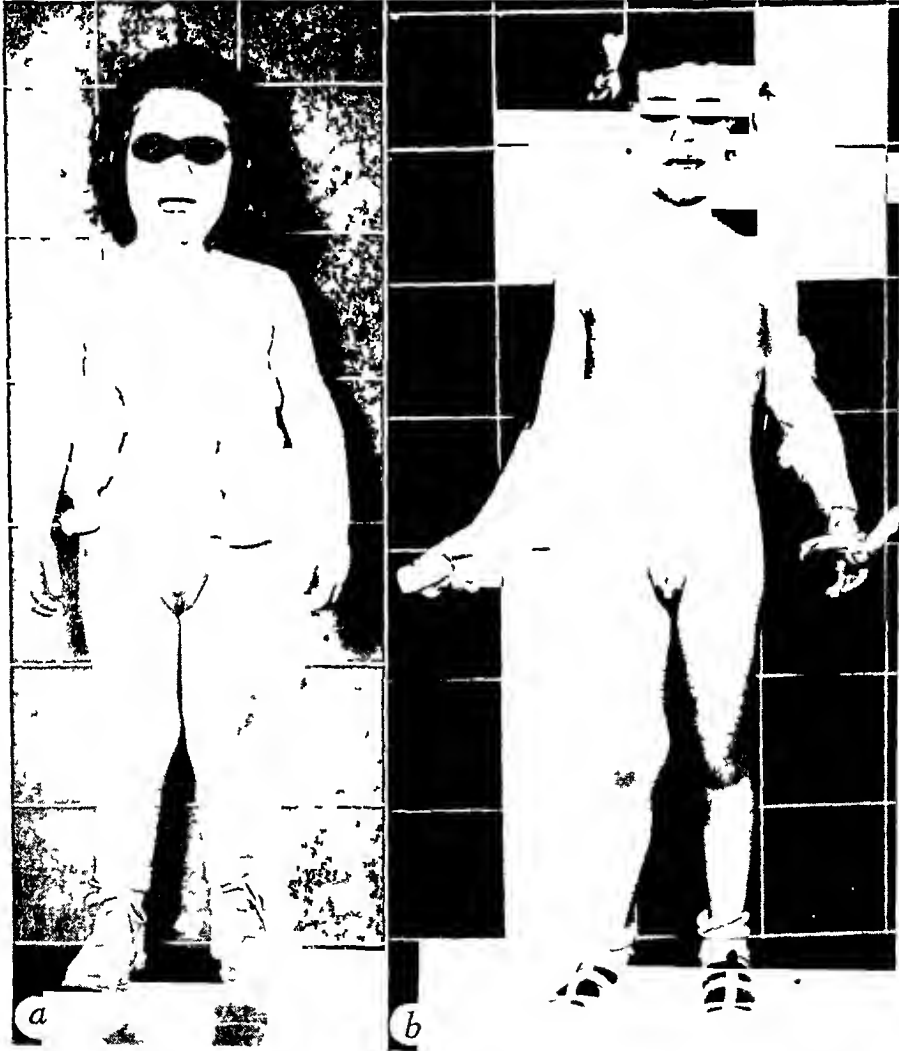


FIG 11 (Case 8)—(a) Immediately following, and (b) six months after removal of the carcinoma of the right adrenal cortex

Physical examination at the clinic revealed that the child had a round face, a slight amount of pubic hair and a clitoris 1 inch (2.5 cm) long (Figs 11a and 12). Otherwise the physical examination gave essentially negative results. Laboratory examination revealed normal urine and 14.1 Gm of hemoglobin per 100 cc of blood. Roentgenograms of the head and thorax showed no abnormality and those of the bones showed development consistent with an age of 45 months. The quantity of 17-ketosteroids excreted in the urine in 24 hours was 62 mg.

The child returned home and was brought back to the clinic for further observation three months later, on December 4, 1947. Symptoms and physical findings had not changed. The urinary excretion of 17-ketosteroids was 6.8 mg. in 24 hours.

The patient was prepared for operation by intramuscular administration of 10 cc. of cortical extract (Kendall) the evening before the operation and of an additional 10 cc. on the morning of the operation. On December 5, 1947, the left adrenal gland was exposed through a posterolumbar incision and found to be a third of the usual size. The right side was then explored and a multilocular tumor of three components, each 2.5 cm. in diameter, was seen and removed. The pathologist reported that the lesion was a semi-encapsulated partly solid and partly cystic hemorrhagic carcinoma of the adrenal cortex of low grade, it weighed 36 Gm.

Following the operation, the child was treated with cortical extract (Kendall) and solutions of sodium chloride and glucose (Table IX). No signs of adrenocortical insufficiency were observed. Her convalescence was uneventful. Ten days after excision of the tumor the urinary excretion of 17-ketosteroids was 0.3 mg. and that of cortin-like substances was 0.165 mg. in 24 hours.

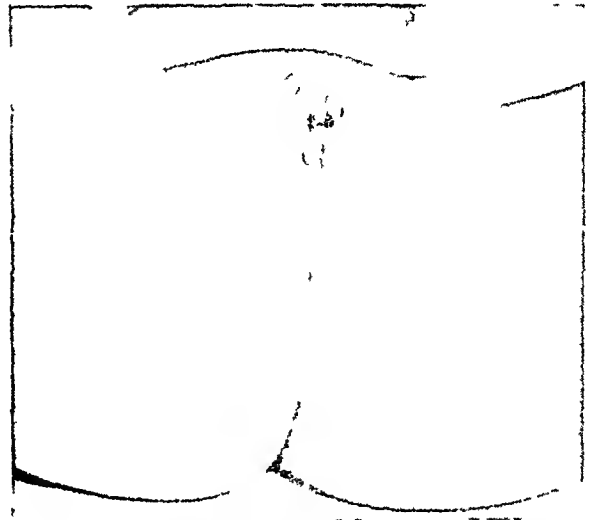


FIG. 12 (Case 8) — Pubic hair and enlargement of the clitoris

TABLE IX — Treatment Before and After Removal of Tumor of the Adrenal Cortex in Case 8

Day	Cortical Extract (Kendall) cc	5 Per Cent Glucose in Physiologic Saline Solution cc	5 Per Cent Solution of Glucose cc
Preoperative			
1	10		
0	10		
Postoperative			
1	35	800	
2	30	200	500
3	30	400	
4	20		
5	20		
6	15		
7	10		
8	5		

On June 8, 1948, the patient was brought back to the clinic. Her mother stated that the child had been in good health except for one bout of nausea and vomiting. There had been a change in her general appearance, so that her face and body habitus were much more slender than formerly (Fig. 11b). The urinary excretion of 17-ketosteroids was 0.

SUMMARY

The clinical pictures associated with hyperfunction of the adrenal cortex are extremely protean in nature and presumably depend upon the type and

the quantity of steroid hormones produced, the age and sex of the patient and perhaps on other factors

For patients presenting clinical syndromes known to be associated with hyperfunction of the adrenal cortex, the problem of differentiating between tumor and hyperplasia has been simplified, though not entirely solved, by methods of urinary assay

The purpose of the present paper is to present a group of eight cases of proved tumors of the adrenal cortex which exemplify some of the problems encountered in diagnosis and surgical treatment. These cases supplement the ten cases reported in 1934 and the seven reported in 1938

At the time of these earlier reports, methods for assay of urinary steroids were either unknown or were in an early stage of development and little was known of the effects of pure adrenal steroid hormones

Desoxycorticosterone has its effect upon salt-and-water metabolism, Compounds A, B, E and F of Kendall on carbohydrate and protein metabolism, and the first two on fat metabolism. Androstenedione and androstosterone, estrone and progesterone have androgenic, estrogenic and progestational effects, respectively

Edema, hypertension and congestive heart failure may result from retention of salt and water and loss of potassium may lead to profound muscular weakness

Overproduction of hormones having physiologic effects like Compound E and Compound F may explain the diabetes mellitus, the negative nitrogen balance, the muscular weakness, the osteoporosis, the thinning of skin and the ecchymosis, and the effect of lymphoid tissue may explain the leukopenia which is characteristic of Cushing's syndrome

Virilism, hirsutism, baldness, amenorrhea, florid skin hypertrophy of the clitoris, acne, masculinization of the voice in women and alteration of the habitus in the direction of masculinity might result from the production of an excessive amount of androgenic material by an adrenocortical tumor—and likewise the occurrence of sexual and somatic precocity in children

Overproduction of estrogens and of compounds having an action like that of progesterone may explain the vaginal bleeding and sexual precocity in girls who have tumors of the adrenal cortex and the occurrence of impotence and gynecomastia in men

Lastly, and of extreme importance, is the fact that a patient with a hyperfunctioning tumor of the adrenal cortex and virilism is likely to excrete a large amount of 17-ketosteroids in the urine and, on the contrary, if evidence of virilism is minimal or lacking, as in Cushing's syndrome, the excretion of 17-ketosteroids may not be elevated

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INDICATIONS AND RESULTS OF SPLENECTOMY*

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IN SPIKE OF THE FACT that much progress has been made in the diagnosis and treatment of splenic disease during the past few decades, there is still considerable controversy in this subject, particularly concerning the indications for splenectomy. Thrombocytopenic purpura illustrates this point well, since in many instances, the disease is of the secondary (symptomatic) type in which splenectomy is rarely effectual.

FUNCTIONS OF THE SPLEEN

The functions of the spleen are but incompletely elucidated, but a knowledge of its function is essential in considering indications and contraindications of splenectomy. More is known of the adverse physiologic effects of a diseased spleen on the organism than of the functions of the normal spleen.

The removal of the normal spleen apparently does not have any detrimental consequences on the general well-being of the patient. Certain of its normal functions which it shares with other hemopoietic organs can be quickly taken over after extirpation of the spleen. On the other hand, the spleen in certain pathologic states may develop unusual importance and even become injurious to life.

Normal Functions of the Spleen. The spleen contains the largest collection of lymphoid tissue in the body and the bulk of the reticulo-endothelial cells. It is intimately concerned with *red blood cell destruction* (almost one trillion per day) and potentially with *blood formation*, although the physiologic mechanism involved in these splenic functions is not known. In *fetal life*, the spleen is active in the *formation of all types of blood cells* and can revert to this function upon demand at any period of life. In the adult this activity is limited to the *production of lymphocytes and monocytes*. The spleen actively participates in the *elimination of erythrocytes* and the products of their disintegration, together with bacteria and other foreign matter. It is interesting to note that this normal process of red blood cell destruction is greatly increased in certain pathologic conditions. In some unknown way the spleen renders *circulating erythrocytes more fragile*. By the reticulo-endothelium of the spleen the hemoglobin from worn-out erythrocytes is converted into bilirubin for passage to the liver.

Much of the iron in the body is stored in the spleen, where it is available for

* Read before the Southern Surgical Association at White Sulphur Springs, W. Va., December 7, 1948.

the elaboration of hemoglobin and the formation of new red blood cells. The spleen, by virtue of its spongy network of pulp elements, serves as a controllable blood reservoir, thus aiding the circulation when demand for blood is increased.

The spleen exerts an *inhibitory action on the hemopoietic function of the bone marrow*, as evidenced by the almost constant occurrence of thrombocytosis and leukocytosis following splenectomy. Other probable functions of the spleen are related to immunity, filtration of bacteria from the blood stream, digestion, metabolism and tumor formation.

Abnormal Functions of the Spleen In reality, the abnormal functions are much more important to the clinician than the normal functions. Most of these abnormal functions are related to overactivity of one or more of the normal functions, thus giving rise to the term *hypersplenism*. The functions most often becoming abnormal or overactive are the inhibiting effect on the bone marrow and the increase in fragility of the red blood cells. If the inhibition on the bone marrow affects platelet formation (which probably is a failure of maturation of megakaryocytes to platelets, secondary to some chemical product formed abnormally by the spleen), thrombocytopenic purpura is produced. In hemolytic anemia the fragility of the erythrocytes, particularly the spherocyte, is increased, thus giving rise to sufficient erythrocytic destruction to produce anemia and jaundice, the latter from increased formation of bilirubin from the hemoglobin of destroyed red cells.

If the bone marrow inhibition is limited to formation of neutrophils (*i.e.* granulocytic maturation), the disease is known as splenic neutropenia.

Various combinations of the above abnormalities are encountered. When all three are present the disease is designated as panhematocytopenia. In Banti's disease, and Felty's disease the inhibition of granulocytic maturation is also present, although in these diseases other abnormal features, as described later, are encountered.

The cellular elements of the blood may be formed in excess by the spleen. When the white cells are involved, one of the types of leukemia will result.

Effects of Removal of the Spleen Removal of the spleen normally results in certain changes in the cellular elements of the blood or changes in the physiology. For example, leukocytosis and thrombocytosis regularly follow splenectomy. These changes reach a peak in 6 to 14 days and then slowly revert to normal. There is also a temporary slight increase in the erythrocyte count. The platelets may increase from a normal figure varying between 200,000 and 400,000 to 1,500,000. If the increase approaches the last figure named, it is desirable to give an anticoagulant such as heparin (Norcross¹), particularly if the splenectomy has been performed for Banti's disease, because thrombosis (venous) and emboli (pulmonic) are so apt to develop. There is no greater tendency for an increase in the platelet count in Banti's disease than any other disease, but the stasis of blood in the portal vein and remnant of the splenic vein makes thrombosis at one of these sites more likely. The effects of splenectomy on bone marrow constituents have been described by Limarzi and associates.²

CO-OPERATION BETWEEN THE SURGEON AND THE HEMATOLOGIST

It is highly essential that close co-operation between the surgeon and the hematologist be maintained with every patient upon whom splenectomy is contemplated, particularly if indications are not definite. As a matter of fact, indications can rarely be classified as positive unless the results of a sternal puncture are known. The necessity of skill in the interpretation of bone marrow smears is the important factor demanding co-operation between the two clinicians mentioned. The technic of sternal puncture and interpretation of smears has been described elsewhere by Limarzi and associates.³

INDICATIONS FOR SPLENECTOMY

1 *Hemolytic Jaundice* There are two types of hemolytic jaundice, namely congenital (familial) and acquired. Because results of splenectomy in the acquired type are so unsatisfactory, it is essential to differentiate between these two conditions. In the *congenital type* several members of a family may be affected, and the condition may be traced back through several generations. In the average case there is little interference with the well-being of the patient except for the marked yellow coloration of the skin and sclera and a slight anemia. Symptoms are occasionally not noted until adult life.

Splenomegaly, jaundice, anemia, microspherocytosis and increased fragility of the red cells in hypotonic salt solution are the prominent manifestations of congenital familial jaundice; reticulocytosis and increased urobilinogenuria are usually noted. The spleen is usually greatly enlarged and may be ten times larger than normal. One-half to two-thirds of the patients have gallstones (Pemberton⁴). The tendency of the spleen to filter out and destroy the spherocytes (consistently present in the disease) is responsible for the jaundice and splenomegaly (Haden⁵). The bone marrow reveals hyperplasia of the myeloid, erythroid and megakaryocytic elements, although in this disease the marrow findings cannot be considered diagnostic. The increase in bone marrow activity results in an increase of nucleated red cells (especially reticulated red cells) up to 10 per cent in the blood.

The manifestations of *acquired hemolytic jaundice* are very similar to those of the congenital type as described above. Acquired hemolytic anemia may result from circulating hemolysins such as may follow the repeated transfusion of an Rh negative patient with Rh positive blood or the activation of a specific hemolysin in some syphilitic persons by exposure to cold, severe burns, bacterial infections (especially those due to anaerobic organisms) or snake venom. Lederer's anemia is an atypical (acquired) type of acute hemolytic anemia secondary to an infectious process. It has been found most commonly following respiratory infections among children. There may be a palpable spleen, spherical microcytosis and increased fragility. Lederer's anemia is corrected by transfusions of blood. Recovery is complete and the condition does not recur. Parasitic infections such as malaria, poisons such as lead or phenylhydrazine and sensitivity to drugs or plants are other etiologic factors which must be considered in the diagnosis. It must be remembered that hemo-

lytic anemia may be a complicating feature of many diseases in which splenomegaly may or may not be a characteristic finding, such as Hodgkin's disease, leukemia, myeloid metaplasia of the spleen (agnogenic myeloid metaplasia of the spleen), lymphosarcoma, carcinomatosis, severe liver damage, dermoid cyst of the ovary, *etc*. Some of these conditions may be associated with a spherocytic type of anemia and increased fragility. It is of importance that the hemolytic process sometimes disappears following treatment of the associated disease, for example, by the removal of a dermoid cyst. Not infrequently (but in less than 50 per cent of cases) splenectomy will effect a cure in acquired hemolytic anemia, but without affecting the underlying primary condition, such as the leukemia, Hodgkin's disease, *etc*.

In 35 cases of hemolytic jaundice studied by Watson,⁶ 20 were of the microcytic type (familial or congenital) and 15 of the macrocytic (secondary or acquired). In only two of the latter group was there increased fragility of the red cells in hypertonic salt solution. In this group of 15 with secondary jaundice, eight were associated with liver disease, three with Hodgkin's disease, two with leukemia, one with hyperthyroidism and one with chronic bleeding into an ovarian cyst.

In hemolytic anemia, transfusions commonly produce severe reactions. This complication gives rise to a serious problem in the treatment of the disease, particularly when an acute hemolytic crisis develops. However, it is now fairly universally agreed to submit patients with the congenital type of hemolytic jaundice to immediate splenectomy if crisis is present, transfusions should be started only at the end of the operation, after the splenic pedicle has been ligated.

Since results are so consistently good and the operative mortality rate so low in the congenital type, this disease represents one in which indications for splenectomy are perhaps stronger than in any other disease. This is particularly true if symptoms, especially anemia, are manifested in childhood, since normal growth and development may be retarded.

2 *Thrombocytopenic Purpura*. In a consideration as to the indications for splenectomy in purpura it is essential to distinguish between primary (Werlhof's) and secondary or symptomatic purpura, since splenectomy is of little or no value in the latter condition which may be secondary to drugs, leukemia, aplastic anemia, radiation (roentgen and radium), tumors, infections, *etc*.

Classical manifestations are prolonged bleeding time, normal coagulation, no clot retraction, low platelet count, anemia, ecchymosis, petechiae and bleeding from mucous membranes or body orifices. The anemia is directly related to the loss of blood and gives rise to such symptoms as weakness, malaise and loss of weight. The tourniquet test (blood pressure cuff on arm at diastolic pressure for five minutes) is positive. Details of differential diagnosis and bone marrow studies have been discussed elsewhere (L. R. L.⁷). In essential (primary) thrombocytopenic purpura the spleen is only slightly enlarged. Marked enlargement of the spleen speaks against primary thrombocytopenic purpura.

Bone marrow examination is diagnostic, revealing a marked increase in the number of immature megakaryocytes without platelet production due presum-

ably to an inhibiting effect of the spleen (hypersplenism) on their maturity and release from the bone marrow into the blood stream. In fact, the number of megakaryocytes in the bone marrow is such a reliable indication of true thrombocytopenic purpura that it may be used as an index of prognosis following splenectomy.

The disease has numerous recurring cycles and is rarely seen under the age of 10 or after the age of 40. Hemorrhage (from the uterus, gums, nasal septum, etc.) may be severe and in fact is not uncommonly fatal. The authors are convinced that severe hemorrhage is a strong indication for immediate operation and not a contraindication. Without question the high operative mortality rate noted in such cases in previous years was related to the failure to have enough blood available at the time of operation or the failure to give it. As many as four to six pints of blood may be necessary before the operation is started and as many more during and shortly after operation. Rapid transfusion (of the intra-arterial type) may be indicated when bleeding has progressed to the shock level.

The disease responds so well to splenectomy, and the danger of severe hemorrhage is so great and unpredictable, that some authorities⁸ advise splenectomy in practically all cases, once a definite diagnosis of thrombocytopenic purpura is made.

3 *Banti's Disease* Symptoms vary considerably in this disease, which frequently is difficult to differentiate from cirrhosis of the liver and other diseases of the liver and spleen. The disease has been designated as congestive splenomegaly by Rousselot⁹ because of the portal hypertension produced by obstruction of portal blood in the liver or vein itself.

Important manifestations are splenomegaly, anemia and leukopenia, jaundice and ascites developed relatively late. Fibrosis is present in the spleen and liver, but hepatic cirrhosis is not as pronounced as in the classical atrophic cirrhosis. Adhesions between the spleen and adjacent structures are more dense than in any other disease with splenomegaly. These adhesions are usually vascular, the vessels are venous channels shunting blood from the portal to the systemic circulation. In 43 cases studied by Borg and Duhn,¹⁰ 39 per cent had a history of hematemesis.

Bone marrow findings are variable, depending largely upon the stage of the disease. In the earliest stage the bone marrow shows a myeloid hyperplasia (maturation arrest) and there is a moderate anemia and leukopenia in the peripheral blood. In the last stage of the disease, in which cirrhosis of the liver has developed, the marrow reveals a marked erythroid immaturity as well as a maturation arrest of the myeloid tissue and an increase in the number of megakaryocytes. In a study of 21 cases Limarzi and associates³ noted that the anemia was normocytic in 16, microcytic in three and macrocytic in two. The platelet count was low in six of the 21 cases. The icterus index was elevated in about half.

Opinions vary considerably as to whether or not splenectomy is indicated in this disease. The present authors agree with many authors that splenectomy

may have curative but more often only remedial effects on the disease in early cases. Since hepatic insufficiency exists, as will usually be revealed by hepatic function tests, extensive preparative treatment consisting of transfusions as indicated, high carbohydrate and high protein diet and vitamin supplementation should be instituted before operation is performed.

In the advanced cases we are convinced that the operative mortality rate is so high (5 of 13 in our series) that it outweighs by a large margin any benefit produced by splenectomy. As a matter of fact, it is reasonable to expect that splenectomy would actually be deleterious when vascular adhesions between the spleen and abdominal wall exist, since removal of the spleen would destroy venous channels which carry blood from the engorged portal system to the systemic. We are of the opinion that ligation of the splenic artery, with preservation of the vascular adhesions, would diminish the pressure in the portal system, and portal blood would thus have a better opportunity of gaining access to the systemic circulation. Ligation of the splenic artery is not designed to take the place of splenorenal or portacaval shunt when either of these operations is indicated.

4 *Thrombosis or Anomalous Obstruction of the Splenic Vein* There is controversy as to whether or not this condition should be classified as a separate entity since many observers believe that a large percentage of patients with Banti's disease have some type of obstruction of the portal or perhaps the splenic vein as the etiologic factor. They remark that in the early stages of Banti's disease, as in this condition, the liver shows no change. We have no final opinion as to whether this condition should or should not be included in Banti's disease, but have been unable to produce an hepatic cirrhosis of the Banti's type experimentally¹² by various types of obstruction of the portal and splenic veins, we are therefore inclined to classify this lesion separate from Banti's disease. We have identified five cases in our series as thrombosis or obstruction of the splenic vein, none of which revealed any fibrosis of the liver. However, our impressions are confused by the fact that an additional patient with a liver of normal appearance, and a large spleen at the time of operation, died 18 months after splenectomy with a large liver (without confirmation of autopsy). We classified this patient in the Banti's group, primarily because of the fatal outcome and the unconfirmed report of an enlarged and diseased liver obtained from the attending physician. We are strongly of the opinion that splenectomy in the early stages of splenic vein obstruction should be curative, but equally convinced that splenectomy in early Banti's disease will by no means be curative in all cases.

The manifestations of chronic obstruction of the splenic vein are similar to the manifestations of early Banti's disease, namely splenomegaly with slight and varying degrees of anemia, leukopenia and thrombopenia. Hemorrhage from esophageal varices is common, it was present in all five cases of our series. In the cases with bleeding and many others, roentgen-ray examination of the esophagus with barium will reveal varices. Jaundice was not present in any of our cases. Bone marrow findings are similar to those of early Banti's disease.

In three of our five cases we were fairly certain that the splenic vein was absent or completely obstructed, since no sizable vein could be found even at the hilus. However, as has been emphasized by Whipple,¹³ the presence of obstruction, or its location, can not be accurately demonstrated at operation in more than half the cases unless injection of diodrast into portal tributaries is carried out with the roentgenogram. As stated previously, we believe that splenectomy will be curative in all cases when performed reasonably early in the disease. We are likewise of the opinion that most of the patients with so-called early Banti's disease cured by splenectomy are patients with obstruction of the splenic vein.

5 *Felty's Disease* There is likewise controversy as to whether or not this syndrome as described by Felty¹⁴ nearly 25 years ago is a separate entity. After studying the five cases we have classified as such, we are convinced they cannot be classified in any other group, although in reality they do represent cases of secondary splenic panhematocytopenia. Four of the five cases originally described by Felty had an anemia, whereas all had a neutropenia, there was no record of a platelet count.

The spleen shows reticular hyperplasia and erythrophagocytosis. The bone marrow is usually hypercellular, predominantly involving the granulocytic elements. The usual manifestations are chronic deforming (rheumatoid) arthritis, painful joints, anemia, splenomegaly, leukopenia, cutaneous pigmentation and lymphadenopathy. All of our five cases had an anemia as well as neutropenia, two of them also had a thrombocytopenic purpura. For this reason it appears that our cases, at least, could be classified as splenic panhematocytopenia, but of the secondary type, since the rheumatoid arthritis was an important feature of the disease. Although splenectomy, originally performed by Hanrahan and Miller¹⁵ for the disease in 1932, may not be curative in this disease, there was such definite improvement (at least of temporary nature) in three of our five cases that we recommend it if the physical condition of the patient permits.

6 *Splenic Neutropenia* This is a relatively rare condition, described in 1939 by Wiseman and Doan,¹⁶ consisting of splenomegaly and peripheral granulopenia. The disease probably represents a selective form of hypersplenism in which the splenic hormones have a deleterious effect on the maturation and delivery of granulocytes from the bone marrow to the blood. The bone marrow, in most cases, reveals a myeloid hyperplasia, which must be demonstrated before splenectomy is advised. According to Wiseman and Doan, the spleen shows clasmatoctosis with excessive phagocytosis of granulocytes. Results of splenectomy will be very good if the bone marrow shows a normal or increased number of normally developing granulocytes in the bone marrow.

7 *Primary Splenic Panhematocytopenia* This is likewise a rare disease¹⁷ which responds very well to splenectomy. It may be congenital, acute or even secondary to such conditions as Hodgkin's disease, drug sensitization, Gaucher's disease, etc. The disease also represents a type of hypersplenism in which the splenic hormonal functions become exaggerated and result in an inhibitory

effect on the maturation and delivery of granulocytes, erythrocytes and platelets from the bone marrow to the blood. In some cases the spleen at the same time destroys red blood cells excessively, thus, a hemolytic component may be added to the three factors just mentioned. Examination of the peripheral blood reveals a neutropenia, anemia and thrombopenia, or in others words a pancytopenia results. Figuratively speaking, the disease is therefore a combination of hemolytic anemia, purpura and neutropenia. Bone marrow smears show a hyperplasia of all marrow elements with normoblasts predominating. These marrow findings must be demonstrable before a splenectomy is advised.

8 *Rupture of the Spleen* This injury is, of course, an indication for splenectomy but since it involves no controversial points in the physiologic mechanism of the spleen, it will not be discussed, and our cases will not be reviewed herein.

9 *Cysts, Primary Tumors and Abscesses* These lesions constitute a fairly definite indication for splenectomy, although a definite diagnosis can usually be made only by exclusion, and then not with a high degree of accuracy. In a review of this subject, Fowler¹⁸ has noted that some cysts are true cysts of the dermoid or lymphangiomatous type whereas the majority (about 80 per cent) are false cysts of the hemorrhagic type caused by trauma, inflammation or parasites. *Abscess* of the spleen is extremely rare and difficult to diagnose. If the spleen is not densely adherent, it should be removed, otherwise drainage may be the procedure of choice, particularly if it is not necessary to drain across the free peritoneal cavity.

MISCELLANEOUS CONDITIONS FOR WHICH SPLENECTOMY MAY BE INDICATED

Of this group of lesions, *Gaucher's disease* is probably the most important. The primary pathologic feature of this disease is deposition of a large amount of lipid material in the spleen, bone and lymph nodes. Important manifestations are splenomegaly, anemia, and pigmentation of the skin, especially over the face and neck, the disease is usually observed in young girls. Late in the disease a large liver develops. Reticular cells and foam cells in the bone marrow are fairly diagnostic. The bone marrow appears to be just as important in the etiology as is the spleen, which explains why splenectomy is only palliative. Occasionally panhematopenia develops, on which occasion splenectomy is definitely indicated. In the absence of this complication, splenectomy is rarely indicated in late cases.

Not infrequently in massive operations for malignant tumors such as carcinoma of the cardiac end of the stomach, the operation is made much easier if the spleen is removed with the stomach and omentum.

Ptosis of the spleen is occasionally an indication for its removal, but usually only when it is enlarged by some secondary process as it was in one of our patients with early Banti's disease.

Occasionally *malaria* constitutes an indication for splenectomy but only when the disease is completely eradicated and the residual enlargement of the spleen is so marked as to give rise to symptoms because of its size. When recurring

attacks of malaria develop in spite of adequate therapy, and a large spleen is present, it may be justifiable to remove the organ, hoping to eliminate the site where the malarial organisms remain and give rise to recurrent attacks

It should be emphasized that it has been largely through trial and error for many years past that indications and contraindications have been clarified. However, it is true that during the past few years the range of indications has increased slightly to include lesions in which splenectomy can be considered only as palliative. This has been brought about through improvements in surgical skill and anesthetic technic, better preoperative and postoperative care and the use of massive transfusions, sulfonamides and penicillin.

CONTRAINDICATIONS FOR SPLENECTOMY

Perniciou anemia, Hodgkin's disease, leukemia and polycythemia are diseases for which splenectomy is contraindicated. The same may be said for *agnogenic myeloid metaplasia* (myeloid metaplasia of the spleen) although we have one patient in our series of splenectomies classified as such. The reports on the value of splenectomy in cases of sickle cell anemia have been contradictory. In the hypertrophic stage, splenectomy has been recommended. We have observed no clinical or hematologic benefit from splenectomy in a case reported herein and in another case observed before the date when this series was started. Splenic enlargement of the *acute splenic tumor* type, so commonly seen in certain acute infections, is a definite contraindication for splenectomy. Splenomegaly due to such parasites as those encountered in *trichinosis, filariasis, kala-azar* and *distomatiasis* constitute contraindications, although splenectomy in echinococcus disease may occasionally be justified. Obviously, there is no justification for splenectomy for *metastases* of malignant tumors.

IMPORTANT POINTS IN THE TECHNIC OF SPLENECTOMY

It is not our intention to discuss technic in this presentation, although we do wish to emphasize a few of the important features of the operation. The details of splenectomy have been presented elsewhere by one of us (W. H. C.¹⁹). The authors appreciate that any operation may be performed through a variety of incisions, but have given up the paramedian incision because exposure is so poor, particularly on the lateral side. We have adopted an incision which starts at the ensiform cartilage as a left paramedian incision, proceeds downward and across the rectus muscle, thence laterally, parallel to the costal margin. The Singleton incision,²⁰ which may be classified as an oblique transverse incision, starts in the midepigastrie line half way between the ensiform and umbilicus, retracting the rectus to the right without cutting it. Our objection to this incision is that exposure is very poor just under the diaphragm, where large vessels are constant in the upper portion of the gastrosplenic ligament, and in the diaphragmatic attachment when portal hypertension exists. Any of the oblique transverse incisions, including the one preferred by us, will sacrifice the eleventh spinal nerve, but no paralysis will result from section of just one spinal nerve. The twelfth can readily be retracted laterally and preserved. When the spleen is large we have found it to be of great advantage,

and frequently a relief to the surgeon's blood pressure, to ligate the splenic artery as practiced by Singleton and many others. The artery can be secured through an opening in the gastrohepatic omentum, but we have found it more desirable to ligate it at the superior border of the pancreas, where it is found readily after incision through the thin posterior peritoneum. When the artery is large, as will be the case when the spleen is large, exposure of the vessel will be most readily obtained. A great advantage of preliminary ligation lies in the fact that the spleen is emptied of its blood during manipulation incident to its mobilization, thus supplying an autogenous transfusion. The fascia in any incision for splenectomy should be closed with silk or cotton. We have had no wound separations or hernias following use of the incision as described herein. A thoraco-abdominal incision makes splenectomy easier and in difficult cases will often be justifiable.

RESULTS OF SPLENECTOMY

The operative mortality following splenectomy will vary moderately, depending to a great extent upon the number of patients in the series having Banti's disease. It has been noted by practically all authors, as indicated below, that the mortality is much greater in Banti's disease than in any lesion for which splenectomy is performed. In our total series of 87 splenectomies during the past ten years, we had seven deaths, constituting a mortality of 8.0 per cent. Haden reports an operative mortality of 14 per cent in 56 splenectomies, closely resembling a rate of 16.6 per cent in 30 patients reported by Singleton. Lahey and Norcross report a remarkably low death rate of 2.2 per cent in 83 patients. All the above figures are related to splenic disease and do not include patients operated upon for rupture of the spleen, nor patients in whom splenectomy was performed for malignant disease of some adjacent organ.

Hemolytic Anemia. In our series of 28 patients having splenectomy for hemolytic anemia, 23 were classified as congenital or familial, the results in all of this group can be classified as good to excellent. In congenital hemolytic jaundice the spherocytes function normally after splenectomy, thus explaining why removal of the spleen relieves the jaundice (Haden⁵).

In our series of hemolytic anemias there were five cases of atypical ("acquired") hemolytic anemia of unknown cause, results in this group are very poor. In the *first case*, splenectomy was performed in a six-months-old infant with acute hemolytic anemia with an erythroblastosis that failed to respond to blood transfusions prior to removal of the spleen. The boy is now approximately eight years old and presents the blood findings of a chronic hemolytic anemia. Spherocytosis and increased fragility of the red blood cells have not been observed. The clinical and hematologic findings are not those of Cooley's or Mediterranean anemia. The result is classified as poor.

The *second case* is that of a 56-year-old white female with splenomegaly, jaundice and chronic hemolytic anemia, who was subjected to splenectomy in 1939. She gave a history of frequent upper respiratory infections and temperature elevations. Following the removal of the spleen the hemolytic process subsided but the anemia was only moderately improved. This case probably

represents an acquired hemolytic anemia on an infectious basis. Although splenectomy apparently corrected the hemolytic component, the infection which was still present suppressed the bone marrow erythropoiesis. Chemotherapy had little effect on her phases of temperature elevation which was never absolutely explained. She died in 1948.

The *third case* was a four-year-old white girl with acute hemolytic anemia (red blood count as low as 990,000 and a reticulocytosis of 90 per cent) in whom the erythrocytes and hemoglobin failed to show any appreciable rise with repeated transfusions. She was splenectomized with no immediate postoperative difficulty. There was a temporary but definite improvement in the hemolytic process. Two weeks following the operation she suddenly became worse and died 24 hours later with what appeared to be a recurrence of the acute hemolytic process.

The *fourth case* of acquired hemolytic anemia was a white girl, 15 years of age, in whom autohemolysins were demonstrated (Doctor Davidsohn) during a hemolytic crisis. During the subsiding crisis, which was not associated with an increase in the hemolysin titre, splenectomy was performed. There was an increased fragility of the red blood cells but no microspherocytosis. The hemolytic process showed little improvement following the removal of the spleen. At the present time the hemolytic condition is unchanged, jaundice has become more intense and the liver is now palpable.

The *fifth case* of acquired hemolytic anemia is that of a white female, 19 years of age, who suddenly became ill with an upper respiratory infection and developed extreme weakness and jaundice. An anemia was discovered, for which she received 21 transfusions over a period of two weeks, before she was admitted to the Research and Educational Hospitals. There was no history of taking any medication prior to the onset of the jaundice. Although the reticulocyte count was 17 per cent, microspherocytosis and increased fragility of the erythrocytes were absent. It was thought that the numerous transfusions may have obscured a true spherocytic anemia. The spleen, which was two to three times normal size (300 Gm.) along with several small accessory spleens, was removed shortly after the patient was admitted to the hospital. Repeated transfusions postoperatively helped to elevate the hemoglobin and red blood count. However, shortly after the postoperative transfusions had lost their effect, the hemolytic process became as marked as prior to removal of the spleen. Over a period of three and one-half months following splenectomy, the patient received approximately 15 transfusions of 500 cc. each, as well as a course of streptomycin for an undetermined fever that was associated with pain and tenderness over a palpable liver. The patient was type A, Rh positive, but this was not held to be entirely accurate because of the number of transfusions she had received and it was decided to give her type O, Rh negative blood. It is interesting to note that it was finally necessary to give the patient type A, Rh negative blood, because type O Rh negative blood that was available was incompatible. She finally made an uneventful recovery and has remained well up to the present time.

Thus, of the five cases of atypical or acquired hemolytic anemia having splenectomy, two have died, of the remaining three, only one has finally had a complete recovery from the unknown hemolytic process. These cases serve to emphasize an important point, namely, that in patients with acute and chronic *acquired* hemolytic anemias, the prognosis is poor and the mortality high. This corresponds almost entirely with the experience of Lahey and Norcross, who report splenectomy in six patients with hemolytic anemia, but excellent results in only one. However, good results do follow splenectomy in such cases in a few instances, perhaps in a greater percentage than indicated by our results.

At operation the surgeon must search carefully for accessory spleens, as has been emphasized by Curtis and associates.²¹ Persistence or recurrence of symptoms may be ascribed to the presence of accessory spleens.

2 *Thrombocytopenic Purpura* In our series of 26 patients having splenectomy for thrombocytopenic purpura, we had no operative mortality. Results were classified as good to excellent in 23 of the 26. In the remaining three, results were classified as fair to good. One of these had relief from purpura, but died a couple of years later with pulmonary tuberculosis. The other two had good symptomatic but poor hematologic results.

Lahey and Norcross report a recurrence in three of 17 patients having splenectomy for purpura. In two, the response of platelet rise was slow at first but later was fast. Wintrobe reports 16 splenectomies for purpura, three of whom died in the hospital, constituting operative deaths. All but one of the remainder improved sharply. In these 13 patients followed after operation, the platelets rose rapidly in nine, but rose slowly in four.

As indicated in hemolytic anemia, the operator must search the field around the hilus of the spleen and adjacent areas for accessory spleens. If there is recurrence, thought must always be given to the possibility of a remaining accessory spleen, as has been emphasized by Curtis and associates.

3 *Banti's Disease* In our series of 13 patients classified as Banti's disease, we had five operative deaths. Practically all authors reporting mortality rates have had the same experience, namely that nearly all operative deaths occur in this group.

Our operative mortality for this group is probably higher than others, largely because we have split it into two groups, one of which is listed below as obstruction, or anomalies of the splenic vein, in these patients the mortality will be very low. Four of the five patients listed as operative fatalities died of postoperative hemorrhage. One died of pneumonia and liver insufficiency.

One patient is listed as having only a fair result because of symptoms of cirrhosis, another is still having hemorrhages from esophageal varices. One patient died two years after splenectomy, and another 18 months after splenectomy. We were unable to follow two others. The results in the remaining two patients can be classified as good to excellent. In other words, only two of the 11 patients followed with Banti's disease can be classified as having had good to excellent results from splenectomy.

Borg and Dulin report six operative deaths in 22 cases. Three of these died

of postoperative hemorrhage Lahey and Norcross report splenectomy in 25 patients with Banti's disease with an operative mortality of only eight per cent In their series of 12 patients having bleeding from esophageal varices before operation only three had recurrences

4 *Thrombosis or Anomalous Obstruction of the Splenic Vein* There were five patients in our series which we described as having obstruction of the splenic vein of one type or another As stated previously, many authors include this group of patients in with their patients with Banti's disease We have separated them largely because there is such marked difference in the results of this group from the Banti's group described above All five of our patients in this group had hemorrhage before operation Four of the five patients had an excellent result with no history of hemorrhage since operation One listed as having a fair to good result had two attacks of hemorrhage shortly after splenectomy, but has not had any hemorrhage for the past two or three years Very significant is the fact that even though splenectomy has relieved the patients of hemorrhage in at least four of the five cases, roentgen-ray examination with barium still shows varices present in all

5 *Felty's Disease* We had no operative mortality in the five patients diagnosed as Felty's disease However, one patient died about two years after splenectomy, autopsy revealed a malignant tumor of the thymus The remaining four patients had excellent results although one has had splenectomy so recently (six months) that final results are not definite It should be added that, although the symptomatic and hematologic results are good in these patients, there has been very little improvement in their arthritis

6 *Splenic Neutropenia* We have had no patients which we have identified in this group However, the hematologic data suggest that results should be excellent in the vast majority of patients Preliminary reports from Doan and associates reveal good results after splenectomy in this condition

7 *Primary Splenic Panhematocytopenia* We have likewise had no patients in our series classified in this group However, it is very possible that our five patients classified as Felty's disease could or should be classified as panhematocytopenia, but of the secondary type For example, Lahey and Norcross classify patients with anemia, neutropenia and thrombocytopenic purpura with rheumatoid arthritis as patients with secondary panhematocytopenia Likewise, in this condition results should be excellent in the great majority of patients

8 *Results in Miscellaneous Types of Splenomegaly* Table 1 reveals the fact that we have performed splenectomy in ten miscellaneous conditions, some of which had contraindications or doubtful indications One patient had splenectomy for a cyst of the spleen and one for aneurysm of the splenic artery, with excellent results The results in one patient with Gaucher's disease and one patient with Hodgkin's disease are classified as fair, but only 12 and 18 months, respectively, have elapsed since splenectomy One patient with sickle cell anemia and another with atypical hemolytic anemia have had no improvement since splenectomy One patient operated on for anemia and

hyperplastic bone marrow of uncertain etiology later showed a myeloid leukemia (aleukemic) The patient is feeling better since splenectomy, but only one year has elapsed since operation and a fatal outcome is expected soon The patient with atypical aplastic anemia died on the eleventh postoperative

TABLE I—Types of Patients for Whom Splenectomy Was Performed
(Illinois Research and Educational Hospitals, 1936-1948)

Disease	Results						Remarks
	No of Cases	Good	Fair	Poor	Died after left Hos- Oper pital Death		
Hemolytic jaundice	28	24	1	2	2	1	5 of this group were acquired hem an emia 1 died 9 yrs after op 1 op death 2 poor result
Purpura	26	23	3				1 died of tuberculosis after splenectomy but relieved of purpura 2 had good clinical but poor hematologic result
Banti s disease	13	2	1	1	2	5	4 op deaths due to postop hem 1 fair result with symps of cirrhosis 1 died 2 yrs p o with hem , 1 poor result still bleeding 1 died 18 mo large liver 2 not followed
Obstruction of splenic vein	5	4	1				All 5 cases had preop hem but only 1 has had postop hem X-ray still shows varices
Felty s disease (Sec panhematocytopenia)	5	4			1		1 patient died 1 yr later with malig thymoma 3 patients had little or no im provement in arthritis
Congenital cyst	1	1					
Aneurysm splenic artery	1	1					
Gaucher s disease	1		1				Only 1 year since splenectomy
Hodgkin s disease	1		1				Alive and well 18 mos after operation
Sickle cell anemia	1		1				
Atypical hemolytic anemia	1		1				
Myeloid leukemia	1		1				At time of op patient had anemia and hyperplastic bone marrow—now shows leukemia
Atypical aplastic anemia	1					1	Died on 11th postop day of cerebral hemorrhage
Agnogenic myeloid metaplasia	1				1		Patient had hemolytic process with cel lular bone marrow but preop diag not possible
Splenomegaly and anemia of unknown cause	1		1				

day of a cerebral hemorrhage In this case there was no evidence of regeneration of platelets following splenectomy We operated on one patient with agnogenic myeloid metaplasia, which in reality is a contraindication to splenectomy It is well known that it is extremely difficult to make this diagnosis

until a section of the spleen is obtainable. Operation was performed in this case without a positive diagnosis, but because she had a hemolytic process with a cellular bone marrow showing a normoblastic reaction in keeping with a hemolytic process. She died three months after operation with a pericarditis. One patient with splenomegaly, anemia and gastric hemorrhage of unknown etiology had a splenectomy with no improvement in symptoms.

SUMMARY

The results in four or five of the diseases for which splenectomy is performed are very good, but are markedly dependent upon the choice of patients. The best results are obtained in hemolytic jaundice and thrombocytopenic purpura, but even in these diseases extreme care must be exercised in selecting the patient. So important are the indications for splenectomy that close co-oper-

TABLE II—Mortality Rate in Splenectomy

Disease	No of Cases	Oper Deaths
Hemolytic jaundice	28	1
Thrombocytopenic purpura	26	0
Banti's disease	13	5
Obstruction splenic vein	5	0
Felty's disease (See panhematocytopenia)	5	0
Miscellaneous diseases (Cyst Gaucher's disease atypical aplastic anemia etc.)	10	1
Total	87	7
Operative mortality rate 8.0 per cent		

ation between the surgeon and hematologist is essential. The data herein presented were obtained from our study of 87 patients having had splenectomy during the past 12 years.

It is frequently very difficult to differentiate congenital hemolytic jaundice, in which splenectomy is so universally successful, from acquired hemolytic jaundice in which poor results are so common. The anemia in the former condition is microcytic and in the latter macrocytic. In many of the patients with acquired anemia there is no increase in fragility of the red cells. In 28 patients with hemolytic anemia, results were good to excellent in 23 having the congenital type, but were good in only one of five having acquired hemolytic anemia.

Although results will be good in fully 90 per cent of patients having splenectomy for thrombocytopenic purpura, they will rarely be good in secondary or symptomatic purpura. The best means of differentiation between these two conditions is by bone marrow studies. A marked increase in megakaryocytes is indicative of thrombocytopenic purpura, this feature is of great prognostic value. In 23 of 26 patients having splenectomy for thrombocytopenic purpura,

results were good to excellent in 23, and fair to good in three. There were no operative deaths in this group.

We encountered 13 patients which we classified as Banti's disease and five in whom we considered obstruction (anomalous or thrombotic) of the splenic vein to be the primary cause of the splenomegaly and portal hypertension. Some authors classify these two groups as one, namely portal hypertension, but we prefer to separate them into the two groups mentioned, since the results are so different. Of 13 patients having Banti's disease we lost five following splenectomy. In only two were results good. In contrast, four of five cases with obstruction of the splenic vein had good results following splenectomy. The fifth case is still having occasional hemorrhages from esophageal varices, a portacaval shunt is contemplated in this patient. We are now convinced that splenectomy should be performed in Banti's disease only in its early stages.

Good results were obtained in four out of five patients having Felty's disease, which may also be classified as secondary panhematocytopenia, although there was very little improvement in the arthritis. The fifth case died of a malignant thymoma one year after splenectomy.

We have had no patients with primary splenic neutropenia or primary splenic panhematocytopenia, but Doan and associates report good results in their cases.

In our entire series of 87 patients upon whom we performed splenectomy we had seven operative deaths (8 per cent mortality). Five of these seven deaths occurred in Banti's disease, indicating that careful study must be made in this disease and splenectomy not be performed if hepatic insufficiency or other significant complications are present.

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DISCUSSION—DR LON GROVE, Atlanta I have before me a summary of a personal experience in 52 consecutive splenectomies, covering a period of 20 years from 1927 to 1948 Four of these were done for trauma and will not be discussed

Our results in the remaining 48 cases parallel very closely the experience related by Doctor Cole I might say here that we are thoroughly in accord with what Doctor Cole said about the absolute necessity of having a hematologist of experience associated with you on these cases I do not see how anyone could approach this type of surgery without the help of a really experienced hematologist All these cases have been studied by a hematologist of experience, most of them by Dr Roy Kracke

Twenty of this series were diagnosed as familial jaundice but now, in the light of subsequent follow-up, we should change the diagnosis in one patient to acquired jaundice, because she has not done well

In the purpuras, 13 were diagnosed as idiopathic or primary purpura and one as secondary, and we would like to give in some detail the history of this latter patient This case of secondary purpura was under observation for a long time Even though she showed all the clinical and laboratory findings that would fit a primary purpura, including repeated bone marrow studies, with a history of two sisters and one brother having died with the disease, we were very hesitant to classify her as a primary purpura She responded to no form of conservative treatment and finally was splenectomized She did well for a time, but returned in nine months with all the symptoms she had shown primarily, and died from a subdural hemorrhage

There have been nine patients with Banti's syndrome, two of whom we have lost track of Of the remaining seven, we know five have had subsequent hemorrhages and, of that five, three have died It is interesting that one of these patients went nine years before he had his first hemorrhage, this occurred approximately a year and a half ago and he has not hemorrhaged since This is a poor showing in Banti's syndrome As you see from the age incidence most of these patients were children, the oldest was aged 28 years and the youngest 7 weeks We believe that most of them were diagnosed early but, notwithstanding, they have not done well

The patient with tumor-fibroangioma was reported before this Association at Biloxi in 1936. At that time she was four months of age. She has developed normally, has shown no evidence of metastases, and I believe we are justified in classifying her as a true fibroangioma.

There was one case with so-called primary tuberculosis with no demonstrable evidence of a primary lesion. She was operated upon because of the enormous size of the spleen. She made a good convalescence and did well for two years, then declined rapidly with evidence of miliary tuberculosis and died.

In the pancytopenia purpuras our experience has been the same as Doctor Cole's. One patient died after six months, one died after five years, in another hospital, we were unable to get an autopsy but were informed that the diagnosis was atypical leukemia. The third patient still shows some evidence of anemia with occasional hemorrhage from the gastrointestinal tract. We have had difficulty in evaluating this case, however, because she has a severe radiation proctitis from which she bleeds, and it has been difficult to determine the source of her anemia. She is still living after approximately a year.

As to technic. In adults we have preferred the subcostal incision, while in children we definitely prefer the left rectus incision, as we think it gives adequate exposure. In this group of 48 patients who had splenectomies there were no hospital deaths.

DR. G. T. McCUTCHEEN, Columbia, S. C. I would like to call attention to one fact. I believe internists and hematologists make a distinction between primary splenic disease associated with neutropenia and so-called Felty's syndrome. There has been a very limited number of true Felty's syndrome reported. True Felty's syndrome is characterized by the triad of neutropenia, arthritis and splenomegaly. Recently I was embarrassed by being ignorant on the subject. I saw a patient in consultation with an internist, this woman was 80 years of age and, about eight months before, I had opened a huge abscess on her shoulder. I knew at the time that she had neutropenia but it did not occur to me that she might have Felty's syndrome although she complained of her joints also. The internist had observed her over a long period in an effort to detect an enlarged spleen but could not do so. About three months ago he did find an enlarged spleen, and at that time splenectomy was done. She sailed through it without any trouble and has had no recurrence of boils, her arthritis is better, or improved—apparently sometimes it is more or less permanent—but the neutropenia, which had been persistent for at least a year of observation, within 48 hours returned to normal and has remained so.

I would like to make the distinction that true Felty's syndrome is, I believe, not splenomegaly with neutropenia, but is splenomegaly with neutropenia and arthritis. That is the description given by Felty.

DR. FRANK H. LAHEY, Boston. The mortality of splenic diseases for which splenectomy is done will be controlled much more largely by the hematologist than by the surgeon. The mortality will depend upon how well the cases are selected by the hematologists. The more they deal with these cases the better will the hematologists become in aiding in their selection. The mortality in splenectomies for diseases of the spleen will occur in patients who are in the late stages of Banti's disease in which the operation was probably never indicated, in the cases of hemolytic anemia of the acquired variety, in thrombocytopenias which are not truly idiopathic thrombocytopenias, and in those cases even of idiopathic thrombocytopenia which have been permitted to progress into acute states. The mortality will also be in those cases of secondary pancytopenias in which the spleen has become so large and the patient has progressed into such a state of depletion that any operative procedure will have an associated high degree of risk.

We have just reported in the ANNALS OF SURGERY 83 splenectomies with fatality in only two cases. Both deaths were in patients with late congestive splenomegaly for which the operation probably should never have been done, and occurred before we knew enough about these states to avoid doing operative procedures.

One thing that our experience has taught us is that once the decision is made by the hematologist that the patient with hemolytic anemia, primary neutropenia, idiopathic thrombocytopenia, panhematocytopenia or congestive splenomegaly, is a suitable case for splenectomy, the sooner the operation is performed the better. If one delays, any one of these patients can go into an acute phase of the disease so that the opportunity of doing a splenectomy with almost no risk is lost, and the situation is then approached with a high rate of risk.

Another point I wish to make in connection with our own experience is that hematologists will have to take the responsibility for the very painstaking and intricate determinations as to whether the lesion is really of primary origin or secondary to some other cause for which splenectomy would not in any way be helpful.

I do not know of anything that is more interesting in all these splenic states than secondary panhematocytopenia. It is extremely interesting that anything producing enlargement of the spleen can bring about this panhematocytopenic effect and produce the three common blood changes that one sees in relation to splenic effects upon bone marrow or abnormal red cells, that is, hemolytic anemia, idiopathic thrombocytopenia or secondary neutropenia. It is extremely interesting to realize that even the enlargement which goes with congestive splenomegaly, the tumor infiltration that one sees with Hodgkin's disease, or the enlargement as a result of the infiltration which one sees with Gaucher's disease, can produce these blood abnormalities which individually can occur as abnormal blood states, but in this state, panhematocytopenic effects can all occur in one picture. We do not cure Hodgkin's disease or Gaucher's disease by splenectomy, but we can, temporarily at least, make these patients much better, not only by the removal of the large spleen and its pressure effects but also by doing away with these secondary blood changes which come with these panhematocytopenic effects of enlargement of the spleen.

Regarding Banti's disease, we feel that we may have been hasty in the past in condemning splenectomy entirely. Our only fatalities in splenectomy for congestive splenomegaly have been in those done unwisely in the third stages of the disease. In the early stages we believe that splenectomy still has real value, unless one feels that immediate shunt should be done.

There is one other thing we have said in a paper recently published on this subject, which is a little dangerous to state, but I believe it is sound. When one has a patient with splenomegaly of unknown origin, provided there can be no demonstrated cause for the splenomegaly by a competent hematologist, and it does not occur in a geographic region where malaria and other such diseases are prevalent, then the mortality of splenectomy is so low that we believe splenectomy is indicated. It has been shown that people exist well and without difficulty after splenectomy, and such is the hazard of later changes in blood states due to a large spleen, that we believe, if adequate blood studies have been done and nothing has been found, and the patient is a good risk, splenectomy is justifiable.

DR FRANK WILSON, Birmingham. In the last two years I have had five cases of splenectomy in children at the Children's Hospital in Birmingham. Their ages were four years, two years, 16 months, 15 months and, the youngest, eight weeks. Our experience has been very similar to that of Doctor Cole, in that the hematologist is responsible, to a great extent, for the correct diagnosis in these cases.

One of the cases was a thrombocytopenic purpura, three were familial hemolytic jaundice, and one was diagnosed as acquired hemolytic jaundice. This child was the oldest in the group and at operation the spleen, approximately twice normal size, was removed along with two accessory spleens about 2 centimeters in diameter. All the

children except the last one have been entirely relieved of symptoms. This child has continued to require transfusions with the intervals getting farther and farther apart. We have thought that probably she has another accessory spleen which was not found at the time of operation.

There were two sisters with familial hemolytic jaundice, the older 16 months and the younger eight weeks of age. Their father had his spleen removed at the age of 13 and an aunt also had a splenectomy. The older child's symptoms appeared very early, but as her father was a paratrooper in Germany we waited for his return home before operating on her at 16 months of age. After the father returned, the mother soon became pregnant and the second child, a girl, was born. She obviously had hemolytic jaundice, which was diagnosed soon after birth, and we were unable to keep her blood count up without a transfusion at least once a week.

The mother was much concerned because of the economic phase and the cost of transfusions, and she wanted to know whether or not we could operate on this child as soon as possible. We had never done a splenectomy on a child so young, but we decided to operate on her at the age of eight weeks. The mother is again pregnant and is most anxious to know what can be done for her child and how soon the spleen can be taken out, provided the child is born with familial hemolytic jaundice.

These children upon whom we have operated have all made an uneventful postoperative recovery with no postoperative complications.

We have taken all these spleens out through a subcostal incision, as described by Doctor Cole, with the left shoulder slightly elevated, and I think it makes the operation a great deal less difficult than with a right rectus incision.

DR ROBERT S. SPARKMAN, Dallas. I wish to make a few remarks concerning Gaucher's disease, which Doctor Cole has listed as an occasional indication for splenectomy. Our interest in this condition has been stimulated by the fact that we have four cases of Gaucher's disease under observation at the present time. There are perhaps three very good reasons why Gaucher's disease may constitute a specific indication for splenectomy. The first of these, as has been pointed out by Doctor Lahey, is the fact that patients with Gaucher's disease regularly demonstrate either panhematopenia or one of its components, of which neutropenia is particularly frequent. In fact, in Doan's original report of splenic panhematopenia, one case was in a child with Gaucher's disease. The second reason is the immense size the spleen can attain, one case is reported in which the spleen weighed 7200 grams. This slide shows the size of a spleen in a 5-year-old boy with Gaucher's disease. The third reason is the fact that frequently in children growth becomes completely retarded, to be restored after removal of the spleen.

I offer these as fairly consistent indications for splenectomy in this disease.

DR ARTHUR H. BLAKEMORE, New York. In cases presenting the clinical picture of Banti's syndrome, the surgeon should suspect splenomegaly of the congestive type, and be prepared to locate the site of the obstruction in the portal system. For upon this will depend the correct surgical therapy in a given case of Banti's syndrome.

I make a strong plea that those surgeons interested in splenectomy have a simple venous pressure apparatus boiled up with their instruments in each case. It takes only a few minutes to cannulate an easily accessible, known radicle of the portal vein (e.g., the gastroepiploic) and take a portal pressure reading. If a correct pressure reading thus taken is 150 mm of water or more, it means that the site of portal block is either in the portal vein itself or in the liver. In either case there is portal hypertension not only in the splenic vein but in all other portal radicles as well.

This finding of generalized portal hypertension in association with congestive splenomegaly is by all odds the common finding in cases of Banti's disease. Splenectomy alone will not cure such cases of a tendency to have recurring hemorrhages, whether

they be considered "early" or "late" cases. Our experience at the Spleen Clinic of Presbyterian Hospital, over its nearly 30 years existence, suggests that if a so-called early case of generalized portal hypertension has not had a recurrence of hemorrhage following splenectomy, it simply means that there has not been a sufficient follow-up period. We do not contend that there is not the exceedingly rare case in whom, because of an unusual capacity to develop collateral vessels, hemorrhage may be postponed seemingly indefinitely. But we do not consider that one should necessarily credit splenectomy with the entire role in these rare instances.

Much has been said of splenectomy as removing a burden of blood from the already engorged portal system. In an attempt to evaluate this possible factor we have made some portal pressure readings before and after ligation of the arterial supply while doing splenectomies. The results, so far, have varied from zero to 25 mm (water) change in portal pressure following interruption of arterial blood flow of the spleen. These findings would not seem particularly significant in the usual cases who have portal pressures varying from 300 to 600 mm of water.

The rational attack upon the problem of portal hypertension is the direct lowering of portal blood pressure by the establishment of portacaval shunts. Our experience with this procedure now embraces 75 operations and we are well pleased with the overall results.

In cases of portal hypertension secondary to intrahepatic portal block (cirrhosis) it is our policy to employ the portal vein to venacava type of portacaval shunt, preferably as a side-to-side suture anastomosis. This type of portacaval shunt, because of its large size, is capable of returning the portal pressure to normal and, what is even more gratifying, regularly results in complete disappearance of esophageal varices demonstrable by x-ray. We have accomplished this type of operation with a postoperative mortality of 12.5 per cent. This we think is reasonable when one considers that disease of the liver was present in every case.

The splenorenal type of portacaval shunt, preferably as an end-to-side anastomosis of the splenic vein by suture with the left renal vein (Blalock) is decidedly the next most efficient set of vessels to employ in the establishment of portacaval shunts. The truth of the matter is that conservation of the splenic vein for anastomotic purposes is the one best hope of cure for that large group of portal hypertensives having normal livers, in which the seat of portal block is in the portal vein itself, thus precluding its use for shunting purposes.

In view of the above facts, in cases in which careful hematologic and liver chemistry studies would indicate the likelihood of portal hypertension due to extrahepatic portal block, it is to the best interest of the patient that the surgeon be prepared to make confirmatory portal pressure readings at operation. Certainly it is only by recognizing the presence of portal hypertension when confronted with it (one cannot often tell by the appearance of the veins) that we will ever be able to stop adding to that pathetic group of post-splenectomy bleeders—cases whose best hope may lie in the conservation of the splenic vein for shunting purposes. In such cases if, upon exploration, the surgeon be unprepared to proceed with splenorenal anastomosis at the time, in fairness to the best interest of the patient he should close the abdomen and thus conserve the integrity of the splenic vein for subsequent use.

In closing, I wish to discuss the surgical handling of cases which, in our overall series, constitute decidedly a minority group. I refer specifically to cases of congestive splenomegaly secondary to obstruction of the splenic vein. Pathologically, the obstruction is commonly located in the splenic vein at its junction with the superior mesenteric vein, the result, apparently, of congenital atresia. A more sudden onset, particularly in cases giving a history of trauma, suggests thrombosis as the more likely cause of the obstruction.

Of more importance is the ability to distinguish at the operating table two types of cases in this group. For upon this distinction the correct surgical therapy will depend. Differential portal pressure readings are the practical solution of this problem. In the first place, in a case of suspected congestive splenomegaly a normal portal pressure reading,

when taken from a known branch of the superior mesenteric vein, will rule out the liver and the portal vein as the seat of obstruction. Next, if a reading taken from a distal branch of the splenic vein is elevated this confirms the diagnosis of congestive splenomegaly and localizes the site of obstruction to the splenic vein. As previously stated, there are two types of cases which must be differentiated when the splenic vein is the site of obstruction, namely (1) those identified by elevation of pressure in the splenic vein only—cases in which a simple splenectomy will bring about cure, (2) those identified by elevation of pressure both in the splenic vein and in the coronary system of veins—cases in which, to relieve hypertension in the coronary system of veins, a splenorenal shunt is necessary following splenectomy. To identify this second type at the operating table it is only necessary to pull down the stomach, cannulate a known branch of the coronary vein, and take a third venous pressure reading. If the pressure is higher than normal you know at once that the coronary vein joins the splenic vein at a point distal to the obstruction in the splenic vein itself. The reason for the existence of this second type of case is the anatomic frequency (65 per cent) with which the coronary vein joins the splenic vein.

Early in our experience through venography, we confirmed the existence of these two anatomic types. The importance of these findings was well demonstrated in the case of an 18-year-old girl who had a massive hematemesis three months following a simple splenectomy. A venogram showed a greatly enlarged, tortuous coronary vein joining the splenic vein, in which the latter was obstructed at its junction with the superior mesenteric vein. At the time of splenectomy, had the stump of the splenic vein been anastomosed to the left renal vein, the girl would probably be alive today. It is a fact that branches of the coronary vein anastomose with branches of the esophageal veins and this, most likely, accounted for the hemorrhage in this case.

In cases in which return blood flow is impeded in the coronary system of veins for anatomic reasons it is not logical that simple splenectomy should be of benefit. The facts are that the entire arterial supply for the coronary system of veins is gastric, not splenic. Decompression of the coronary system by shunting is the logical solution in such cases.

CHONDROBLASTIC TUMORS OF BONE BENIGN AND MALIGNANT*†

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CHONDROBLASTIC TUMORS OF BONE arise from a proliferation of cartilage at the epiphyseal line, at or near the age of puberty, and are not frequent in their occurrence. Despite the relative infrequency of these tumors, they are of more than passing surgical interest, since they affect individuals in the prime of life and raise the serious issue of amputation versus more conservative therapy.

The authors⁵ called attention to the roentgenologic and pathologic features of these lesions in 1930 and 1931. Such tumors are vascular and cartilaginous, usually situated on the metaphyseal side of the epiphyseal line. They produce destruction in the cancellous spaces and exhibit an overlying periosteal reaction.

In the early descriptions of this tumor, an occasional case was classed as a cartilaginous growth. Borst¹ illustrated a microscopic picture of such a tumor as being a chondrosarcoma. Kolodny¹¹ cited a similar case as an osteogenic sarcoma. Because of the relationship of giant-cell proliferation about vascular spaces at the margin of these growths and the islands of cartilage that have undergone calcification, a school of thought developed classifying these growths as variants of giant-cell tumors. Bloodgood classified them as malignant variants of giant-cell tumor. Ewing described a case as a metastasizing giant-cell tumor and others as benign calcifying giant-cell tumors. Codman² reported a group of cases as epiphyseal chondromatous giant-cell tumors. In reviewing the literature, one is impressed by the paucity of reported cases and the lack of any fundamental basis for their classification.

The authors, in previous communications, first pointed out that these were epiphyseal-line tumors and that the proliferating tissue was chondroblastic, rather than composed of giant cells. It was also emphasized that some of these patients die of metastases, in spite of amputation, whereas others surviving for over five years were apparently cured following curettage and irradiation. In 1942, Jaffe and Lichtenstein¹⁰ reported a group of these lesions, pointing out the cartilaginous origin of the growths, and proposed the term, "benign chondroblastoma of bone," following the histogenic conception previously proposed by the authors.

It is the purpose of this communication to report the findings of a resurvey and careful follow-up of a series of 25 patients and to indicate that these growths may be either benign or malignant, also, that a careful microscopic

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† Aided by a grant for the follow-up of bone tumors given by U. S. Public Health Service.

study will distinguish between the benign and malignant forms of chondroblastoma

CLINICAL FEATURES

The age incidence, the site of the tumor and the short duration of the clinical course are the outstanding features of this chondroblastic tumor, occurring before the ossification of the epiphyseal line is complete. In our series of cases, the age limits were between 10 and 24 years, as compared with the age distribution of from 13 to 17 years reported by Jaffe and Lichtenstein. On the basis of age alone, therefore, this tumor may be linked with the process of bone growth where ossification, by way of temporary calcified cartilage, is taking place at the adolescent period and the epiphyseal line is undergoing ossification.

The localization of the tumors lends weight to this supposition. The location of these growths is predominantly in the ends of the long bones about the knee joint (the upper tibia and lower femur) and in the upper humerus (Fig 1). The bulk of the tumor is on the shaft side of the epiphyseal line, but the epiphysis is also invaded and the growth may be confined to the epiphysis in some cases.

There is a definite correlation between age and the duration of symptoms. In patients under 20 years of age, the average duration of symptoms is less than five months, while in the occasional patient 30 years of age and over, the disease averages over three years. The duration of symptoms, in general, varies from one to 16 months in our series of cases and from 3 to 12 months in those of other authors. The sequence of events is much alike at all ages and is not distinctive. Pain, tenderness and swelling, followed by lameness in the affected member, are characteristic of the lesion where it occurs in a weight-bearing bone. Occasionally, an effusion in the knee joint suggests the clinical diagnosis of tuberculosis. Pathologic fracture has been a rare compli-

CHONDROBLASTOMA

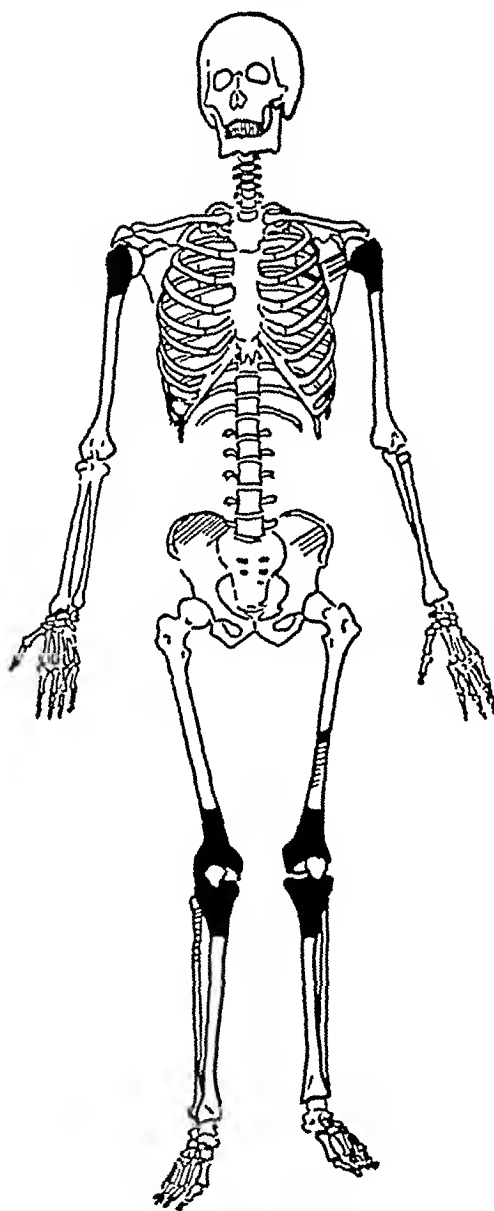


FIG 1—Skeletal distribution of chondroblastoma, benign and malignant. The epiphyseal regions of the upper humerus and the long bones about the knee joints are the most common sites.

cation, occurring only in three instances of our series, although this is clearly a bone-destructive neoplasm. The rarity of this complication may well be attributable to the acuteness of the disease. Fever, leucocytosis and enlargement of the regional lymph nodes are not infrequent in this tumor but may be encountered in cases of other types of bone tumors.

ROENTGENOLOGIC FEATURES

The roentgenologic features of these tumors are fairly distinctive. They produce rarefaction in the cancellous bone, extend on either side of the epiphyseal line and provoke an overlying periosteal reaction, usually along a single



FIG 2



FIG 3

FIG 2—Roentgenogram of a malignant chondroblastoma arising in the epiphysis of the femur, extending into the cancellous bone of the shaft and provoking an overlying periosteal reaction.

FIG 3—Roentgenogram of a benign chondroblastoma involving both the epiphysis and shaft of the humerus. The periosteal reaction, lack of coarse trabeculations, lack of expansion beneath the bone shell, and lack of predominant involvement of the epiphysis help to differentiate chondroblastoma from giant-cell tumor.

margin of the bone (Fig. 2). The extension across the epiphyseal line and the periosteal reaction occur in the early stages of the disease before marked destruction of cancellous and cortical bone has taken place. When the earliest stages of the growth are seen in the roentgenogram, the tumor is usually found to be primary in the metaphysis, suggesting sarcoma. From here it extends to involve the epiphysis in most cases, but rarely invades the bone aggressively in the opposite direction. This peculiarity in the inception of the tumor indicates how intimately it is connected with the growth zones of the long bones which, as is well known, are on the metaphyseal sides of the epiphyseal lines.

While the tumor is predominantly central in location, there is usually an escape beyond the cortex into the subperiosteal region, particularly near the epiphyseal line. In such instances, the periosteum is raised by a translucent shadow, and bone formation from the inner side of the periosteum is noticeably lacking.

In the roentgenogram these tumors differ from benign giant-cell tumors in that they involve both the epiphysis and the shaft of the bone and are not predominantly confined to the epiphysis (Fig 3). They do not expand beneath the shell of cortical bone, nor do they have the coarse trabeculae seen in giant-cell tumors. The periosteal reaction also distinguishes them from benign giant-cell tumors. The age distribution of the chondroblastomas helps in differentiating these growths from benign giant-cell tumors and solitary foci of metastatic carcinoma, which practically always occur after the age of 21 years. Giant-cell tumors occur in the epiphyses of long bones, and cancer deposits that are secondary in bone are localized usually nearer to the midshaft region or at the sites of the entry of nutrient vessels into the bone.

Ewing's tumor may occasionally be a source of confusion. Chondroblastoma which extends into the epiphysis early in the disease can thus be differentiated from Ewing's sarcoma. The periosteal involvement usually extends only along one side of the bone with little or no cortical thickening. While there is a similarity in the age of the patients, in the acuteness of the symptoms and in the tendency to involve long bones, there is, however, in Ewing's sarcoma more formation of new bone, a more diffuse involvement of the shaft, including the midshaft region, together with late involvement of the epiphysis.

The right-angle new bone formation of osteogenic sarcoma is lacking.

GROSS PATHOLOGY

The most important information disclosed by the examination of gross specimens is the continuity between the tumor mass and the unossified epiphy-



FIG 4—A longitudinal section of the amputated specimen represented by the roentgenogram in Fig 2. Note the continuity between the tumor mass and the unossified epiphyseal line. The tumor does not disseminate as rapidly within the cancellous bone as it does in the subperiosteal spaces.

seal line. The foci of invasion of the tumor may extend into the metaphysis or into the epiphysis or laterally into the periosteal zone. However, a connection is always demonstrable between the area in which the epiphyseal cartilage is destroyed and the mass of tumor substance, provided the growth is not too far advanced (Fig. 4).

The mode of extension of the tumor is interesting. In some specimens the unossified epiphyseal line can be clearly traced except at the points where there is proliferation of tumor. Here it is substituted for by a hemorrhagic and necrotic mass which extends in an irregular fashion into the cancellous bone of the metaphyseal region. Very little reactive bone is present. The tumor evidently does not disseminate as readily within the cancellous bone as it does in the subperiosteal spaces, for, once the tumor has invaded the subperiosteal space, a large, proliferating, subperiosteal mass is found.

At operation the tumor may be found extending into the soft parts, covered with a thin envelope of fibrous tissue, invading the subperiosteal regions and surrounded by an intact periosteum or entirely within a bone shell. Most of the neoplasm is usually within the medullary cavity or within cancellous bone. The tumor tissue itself varies in consistency according to the degree of vascularity and necrosis. It is frequently indistinguishable from the hemorrhagic, grumous material found in giant-cell tumor, the hyaline material in chondromas or tissue found in so-called malignant aneurysms of the bone. Small, cystic cavities may be noted in various parts of the tumor.

MICROSCOPIC FEATURES

Under the microscope, chondroblastic tumors are composed of a mass of young and adult cartilage cells undergoing calcification. This tissue differs from normal hyaline cartilage in the vascularity and paucity of the intercellular material. Strands of precartilaginous connective tissue with myxomatous and early fetal cartilage cells are absent. The absence of these cells, along with the vascularity, distinguishes this tumor from the primary and secondary forms of chondromyxosarcoma. The tumor never passes beyond the stage of calcification. There is never any bone of tumor origin, as occasionally is seen in chondromyxosarcoma. Although reactive new bone may be present at the periosteal margins of the chondroblastic tumors, the metastases never show such new bone formation.

A more detailed, high-power microscopic examination reveals the tumor to be composed of polyhedral and angular cells with prominent nuclei and ill-defined cytoplasm. The younger cells have small, dark nuclei, with a crowded chromatin substance, while in the older cells the nuclei are larger and more vesicular, with a distinct central nucleolus. Many of the cells show a prolongation of cytoplasmic processes, and within the meshwork of this reticulation, a clear, faintly stained, intercellular substance is often observed. This apparently represents an attempt at the formation of typical cartilaginous areolae, prior to the stage of calcification.

A characteristic histologic feature of these neoplasms is the intercellular latticework formed by the calcifying matrix. This latticework pervades the tumor, with sketchy, fragmentary, curved lines, emphasized by varying degrees of calcium deposition. Here and there, large areas of uncalcified matrix appear, which are easily recognized as typical hyaline cartilage and, in isolated portions of the tumor, circumscribed islands of chondroblasts may give the tumor an alveolar appearance. The tumor in areas is extremely vascular, with many blood spaces inclosed by a single layer of endothelium. Near these vascularized areas and, usually, toward the periosteal margin of the growth, giant-cell osteoclasts are numerous. These giant cells are of the epulis type and sections cut from the margins of these growths may closely simulate a benign giant-cell tumor and have led, in several instances, to an erroneous diagnosis.

There are two important aspects to the microscopic interpretation of chondroblastic tumors. The first is the distinction of these growths from benign giant-cell tumor. The second is the differentiation of chondroblastic tumors into benign and malignant forms. The presence of chondroblasts and the hyaline matrix, with or without the web of calcification traversing the hyaline material, differentiates these neoplasms from benign giant-cell tumors.

The division of chondroblastic tumors into benign and malignant forms by microscopic study is a more difficult task. Despite the fact that in the roentgenogram the majority of these growths give rise to a periosteal reaction which may suggest an osteogenic sarcoma, it is tragic to recommend a radical procedure if the tumor is benign. It is equally tragic to forego such treatment if the tumor is malignant. We have, therefore, restudied our cases and, through the follow-up reports, have divided the sections into two groups—those remaining well following therapy and those known to have died of the disease. The contrasting features are as follows. In the benign growths the nuclei of the chondroblasts are uniformly small. The cytoplasm is moderate in amount, stains faintly and is ill-defined in its markings. The hyaline matrix is moderate in amount, but infiltrates in fine strands with well-defined reticular fibers. Calcification is usually confined to the matrix (Fig 5). In the malignant growth, the nuclei of the chondroblasts are frequently of large size, bizarre in shape and variable in their staining reactions. Mitotic figures are frequent. The calcification is not confined to the matrix but overlaps the cellular elements unless the section is cut with extreme thinness. Margins of the tumor may show solid islands of chondroblasts arranged in somewhat alveolar fashion, infiltrating fibrous tissue. Much of the tumor is composed of such alveolar masses, with little or no hyaline matrix (Figs 6 and 7). Thus, the distinction between benign and malignant chondroblastic tumors can only be accurately determined by the microscope and by the five-year survival rate and not by the roentgenogram or gross findings.

HISTOGENESIS

In the adolescent period in normal persons, there is at the epiphyseal lines of the upper end of the humerus, lower end of the femur, upper end of the tibia

and lower end of the radius (sites where these tumors predominate) a final spurt of growth previous to the obliteration of the growth disks. This accelerated development in the long bones takes place on the metaphyseal side of the epiphyseal line and is apparently accomplished by a twofold process. There is a reproduction of cartilage cells in the form of chondroblastic proliferation and, in addition to this reproduction, there are maturation and further development of the cartilage cells, terminating in calcification. Later, vascularization with

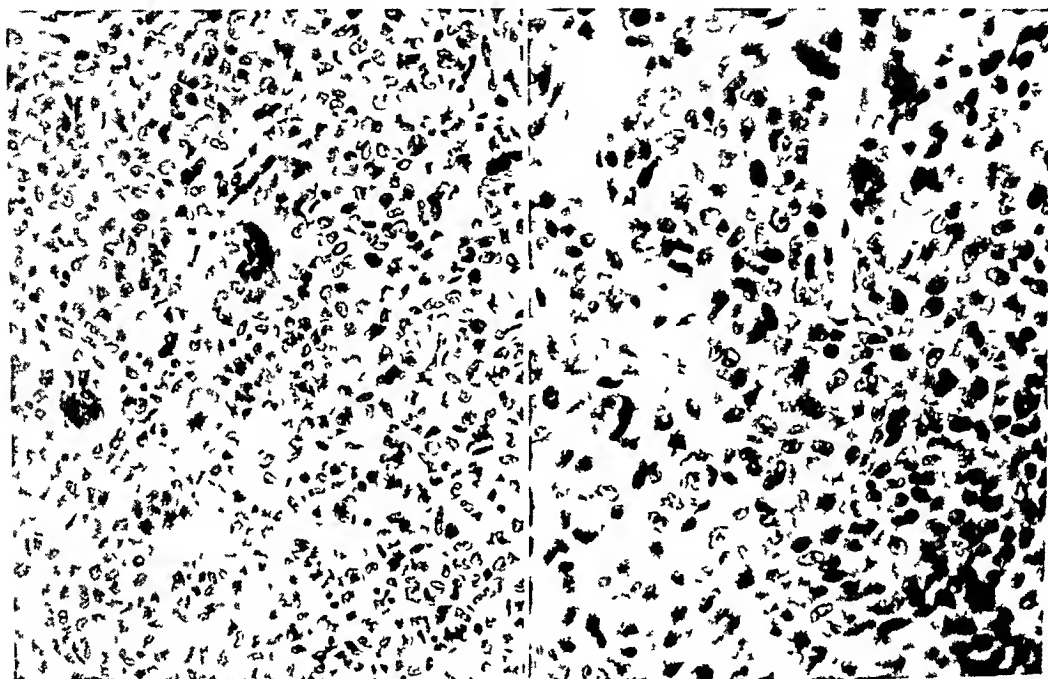


FIG 5

FIG 6

FIG 5—Photomicrograph of a section taken from the benign chondroblastoma shown in Fig 3. The nuclei of the chondroblasts are uniformly small. Near vascularized areas and towards the periosteal margin of the growth, osteoclasts are frequent. Precartilaginous connective tissue and fetal cartilage are absent.

FIG 6—Photomicrograph from the malignant chondroblastoma shown in Fig 2. The nuclei of the chondroblasts are frequently large, bizarre in shape and variable in their staining reaction. Many alveolar masses are seen in some areas. Osteoclasts are present near vascular areas and about the periphery of the tumor. Note: Microscopic examination is the only accurate method of distinguishing benign from malignant chondroblastomas.

resorption of the calcified material takes place, and this is followed by the substitution of permanent new bone. In this final process of substitution, brought about by new blood vessels and the absorptive power of giant-cell osteoclasts, the cartilage cells play no active role but constitute, in their calcified state, a necessary stimulus to final ossification. This entire process, which normally is gradual and orderly, is distorted and hurried by the etiologic factors that precipitate the new growth. This new growth coincides at its inception with the normal developmental process at the epiphyseal line, but

appears to depart from the normal in that an earlier phase of cell proliferation persists, resulting in a preponderance of chondroblastic growth and calcification

The result of this distortion terminates in a tumor process characterized by rapidly proliferating chondroblasts that abort into an end stage of calcified cartilage without producing, except in a fragmentary way, the usual hyaline matrix typical of normal adult cartilage. Apparently, while still in a proliferating stage, many chondroblasts are ensnared in a calcifying matrix of their own making and are petrified.

The vascularity of the tumor and the giant-cell areas are secondary features. That the giant-cell areas in chondroblastic tumors are a product of normal reactive bone, it is believed, is nearer the truth than the supposition that they are a further stage in the osteogenesis of cartilaginous bone by the chondroblasts. Since the death of the chondroblasts, with a formation of a calcified matrix, can be observed under the microscope, it is difficult to see how they could survive to initiate the giant-cell phase. Giant-cell invasion followed by vascular channels is the normal order of osteogenesis in the long bones. The fact that giant cells and vascular channels are more numerous at the margins of the tumor and surrounding normal reactive bone supports this view. Some of the vascularity, however, must be looked upon as a feature common to rapidly growing tumors in general. The presence of vascular foci with giant cells accounts for the frequent mistakes by competent pathologists in diagnosing these neoplasms as benign giant-cell tumors. The classification of these tumors by Codman as "benign epiphyseal chondromatous giant-cell tumors," peculiar to the upper end of the humerus, seems erroneous when the following factors are considered: (1) Chondroblastomas have a wider distribution than Codman indicated and there are proved instances of death with pulmonary metastases, in spite of radical operation. (2) The cartilage present cannot be considered as a passive structure, representing the normal, unossified epiphyseal line. The chondral elements are actively proliferating and the chondroblasts have definite invasive powers. (3) These chondroblasts and their transitional forms are not characteristic of the normal epiphysis, but resemble the cells seen in the embryo when the skeleton is being preformed in rapidly growing cartilage.

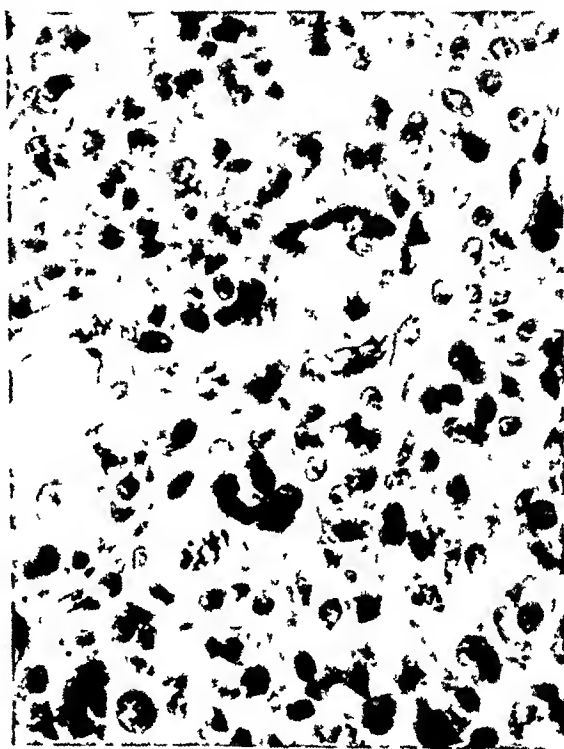


FIG 7—High power micrograph from section shown in Fig 6 illustrating in detail the malignant characteristics which occur in the cellular morphology of the tumor

PROGNOSIS AND TREATMENT

Chondroblastic tumors are a new clinical entity as far as the modern literature is concerned. Few cases have been separated from the categories of chondrosarcoma and atypical giant-cell tumors. To date, the only series available for review are cases studied by the authors, those of Codman, Coley and Santoro and those of Jaffe and Lichtenstein.

The most important aspect of the treatment is the division of the chondroblastic tumors into the benign and the malignant forms on the basis of microscopic studies. Since this is an exceedingly difficult job and since cures have followed curettage, or curettage plus irradiation in the benign form, it is important that radical operations should be postponed until the sections have been reviewed by competent pathologists. Biopsy, followed by roentgen therapy, should be the initial procedure in these growths. The sections should then

TABLE I—*Location of Chondroblastomas in Patients Living Five Years or More, with Treatment Received*

<i>Lower Femur</i>	Three cases treated as follows
1	Biopsy irradiation
2	Curettement irradiation
3	Curettement
<i>Upper Humerus</i>	Five cases treated as follows
1	Irradiation resection
2	Biopsy irradiation
3	Curettement
4	Curettement irradiation administration of Coley's toxins
5	Curettement
<i>Lower Radius</i>	One case treated as follows
1	Curettement Roentgen ray treatment amputation
<i>Upper Tibia</i>	One case treated as follows
1	Biopsy amputation

be submitted to competent pathologists for final diagnosis. Resection or amputation should not be performed unless the malignant nature of the lesion has been verified.

The authors have followed a large, significant series of cases for more than five years. The benign and malignant forms of chondroblastic tumors are in a ratio of 2:3. Of 25 cases studied, 10 proved to have benign chondroblastomas and 15 had the malignant variety of chondroblastoma. The malignant cases usually died within a period of from 9 to 18 months. Among the benign cases followed, all the patients have survived over five years and some are living now more than from 10 to 20 years later. The 10 patients living over five years had lesions as follows: Femur, lower, 3, humerus, upper, 5, radius, lower, 1, upper tibia, 1. (See Table I.)

SUMMARY

Chondroblastic tumors arise from a proliferation of cartilage at the epiphyseal line during the age of puberty and are extremely rare. The tumor occurs most frequently in adolescence, in the region of the epiphyseal line, in the upper end of the tibia, the lower end of the femur and the upper end of

the humerus. In the roentgenogram, there is a mottled area of bone destruction, with or without a slightly expanded bone shell, and, in addition, there is definite periosteal reaction. Under the microscope, these lesions show a proliferation of chondroblasts which produce abortive fragments of calcifying cartilage. At the margin of these tumors, as a defensive reaction, giant cells proliferate and attempt to remove calcified products of the tumor. It is important, in the microscopic diagnosis, to distinguish benign chondroblastic tumors from the malignant chondroblastomas. Patients with benign chondroblastic tumors are well following curettage or curettage with deep roentgen therapy. Malignant chondroblastomas, on the other hand, warrant radical resection or amputation, depending on the site of the tumor. Radical therapy should not be undertaken without submitting the sections for review by a pathologist specializing in bone diseases.

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DISCUSSION.—DR. BRADLEY L. COLEY, New York: This is an important paper, one of a long line of contributions by the team of Geschickter and Copeland. I am glad to see them together again after the interval necessitated by the War.

It seems to me that those who are not particularly experienced in the pathologic interpretation of bone tumors, for example the clinicians, are often confused by the varied terminology applied to these tumors and, in fact, to bone tumors in general. This is unfortunate, because it creates a state of confusion where a phrase meaning one thing to one man has an entirely different meaning for another, and while people in different parts of the country may think they are talking about the same thing this may not be the case.

I agree with everything Doctor Copeland has said about the specific entity or nature of this tumor, which Codman originally described and to which he gave the term epiphyseal chondromatous giant cell tumor. Jaffe and Lichtenstein, who were not convinced that it belonged in the category of giant cell tumor, proposed the term benign chondroblastoma, and Copeland and Geschickter broadened the field to include malignant tumors, calling this specific tumor malignant chondroblastoma. I believe that for those of us who do not

breathe the rarefied atmosphere of the bone pathologists it might be advisable to reserve the term benign chondroblastoma for the tumor in its benign stage, but that when it occurs as a malignant process—which I think is a transition—then it might be given the out-and-out term of chondrosarcoma, thus acquainting the man who is to treat the case with the true nature of the tumor.

In recent years at Memorial Hospital we have been much impressed by the insidious behavior of cartilage tumors, be they of this type or one of those arising in a central chondroma or an osteochondroma. We have seen a considerable number of these benign tumors that have become malignant—after a lapse of time and usually in middle life and sometimes in later life. We believe, therefore, that the adoption of aggressive measures, *i.e.*, complete removal while the tumor is in the benign stage, represents good preventive cancer surgery and will result in saving many lives.

We do not feel that a mere biopsy or curettage followed by roentgen therapy is a desirable method of management. These tumors are usually amenable to complete curettage or resection followed by immediate implantation of bone chips in the cavity. Furthermore, this affords the pathologist an opportunity to study all the available tissue. If he reports it to be malignant then an amputation or resection should be performed. Our experience leads us to decry the use of postoperative or preoperative roentgen therapy for any central cartilaginous neoplasm, regardless of whether it is of the type described in this paper or a simple central chondroma or a frankly sarcomatous one. The unfavorable results obtained, together with the fact that these tumors are definitely known to be radioresistant, militates against this form of treatment.

In closing, we wish to emphasize the misleading nature of the histologic picture. If a report of chondrosarcoma or chondromyxosarcoma is rendered the surgeon may rely upon it, but if the report indicates only chondroma or osteochondroma, then he should regard it as inconclusive. We have in such cases observed metastases long after extirpation of the growth or after amputation. We have become so acutely conscious of the unpredictable nature of benign tumors of cartilage that we are guided more by the clinical features and the roentgenographic appearance than by the histologic findings where the latter indicates that the condition is benign.

We are greatly indebted to the authors for emphasizing the hazards that are presented by one specific variety, *i.e.*, benign chondroblastoma. We suggest that it be called chondroblastoma while it is benign, and chondrosarcoma when it is malignant.

(Slides) The first slide represents a woman in her early 60's with a central cartilaginous tumor, and I defy anyone on clinical or roentgen examination to be certain whether it is benign or malignant. We resected this tumor and the histologic report was low-grade chondrosarcoma. We substituted the upper end of the fibula for the defect in the humerus.

The next slide shows an entirely different type of tumor. I apologize for showing some cases that are not absolutely in line with those shown by Doctor Copeland, but I think they illustrate points I am trying to make about the serious nature of these cartilage lesions. This is a middle-aged Puerto Rican who had an enormous, slowly-growing tumor of the humerus. Note the roentgenographic appearance, especially the marked productive tumor tissue with calcification and atypical bone formation. A biopsy was done at another hospital and our pathologists who reviewed the sections agreed that it was a benign chondroma. Our feeling, however, was that if it were not malignant it was destined to become so, and that radical measures should be adopted. Accordingly a hemipelvectomy was performed. This slide shows the specimen, both the outer aspect and the cut section. The patient made a good recovery and remained well for 20 months, when a checkup film of the chest revealed pulmonary metastasis. The patient is now dying of the disease. Attention is called to the fact that in this case, even when the pathologist had an opportunity to go over the entire specimen and make as many sections as desired, he still reported it to be a benign chondroma.

This final slide shows the humerus of a naval officer who had had five operations by the time we first saw him. We were uncertain of the nature of the lesion because previous microscopic reports had all shown it to be benign chondroma. It was decided, however, to perform a segmental resection and, fortunately, the microscopic examination showed it was still a benign chondroma.

DR MURRAY M COPELAND, Washington (closing) Doctor Geschickter and I have always had great respect for the team of Coley and Coley, now represented by Bradley and through the years we have learned a great deal from both of them. We would take no issue with the main points Doctor Coley has discussed, but we would like to re-emphasize that in this cartilaginous entity, with giant cells, one is put to it frequently to decide whether the lesion is benign or malignant. We do not feel that these lesions are related to central chondromas or ordinary chondrosarcomas. We quite agree that x-ray therapy is not, in general, the treatment of choice in cartilage tumors. For some reason, however, these epiphyseal lesions, namely, chondroblastomas, seem to be more sensitive than the average cartilage tumor and we think it worthwhile to relate the treatment used in the ten cases living five years or more. (See Table in body of paper)

We feel that when the diagnosis is made it is better to treat the lesion surgically by complete curettage followed by cauterization with either 95 per cent alcohol or 50 per cent zinc chloride. Either one of these caustic agents must then be followed with 95 per cent alcohol. We quite agree with Doctor Coley that a single biopsy from these tumors will not rule out malignant changes which may exist in the lesion but that one should have pathologic studies of the entire process.

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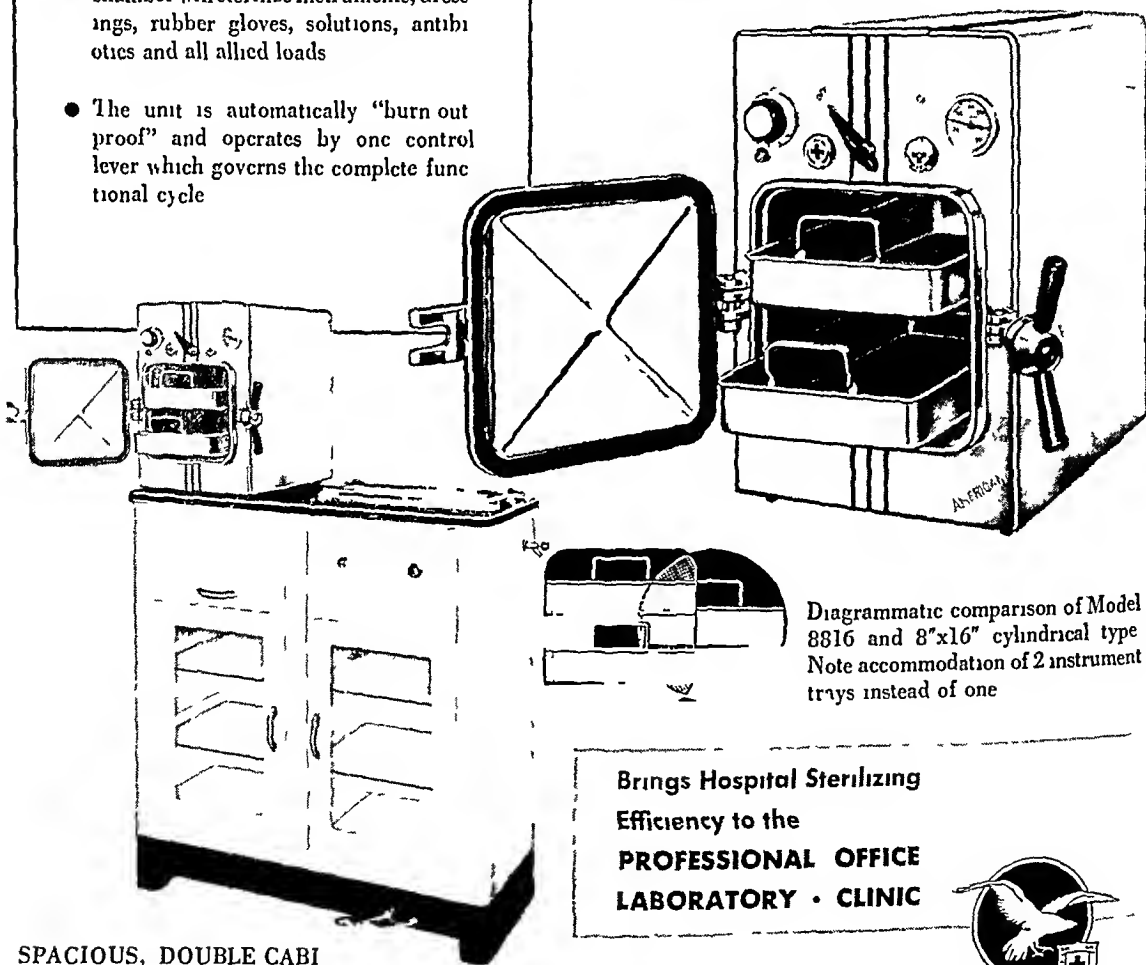
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No 6



CALCIUM DEPOSITS IN THE VICINITY OF THE SHOULDER AND OF OTHER JOINTS*

J ALBERT KEY, M D

FROM THE DEPARTMENT OF SURGERY OF THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
ST LOUIS MISSOURI

THE OCCURRENCE of localized deposits of calcium in the supraspinatus tendon in the floor of the subdeltoid bursa is a well-known clinical condition and during the past 30 years many papers have been published on the subject. This literature is reviewed by Codman¹ and Wilson².

It is not so well known, however, that similar deposits of calcium may occur in the other tendons of the shoulder girdle and in the vicinity of other joints. The only paper that I have found in the American medical literature describing calcium deposits about various joints other than the shoulder is that by Hitchcock,³ in which nine cases are reported. Knee—two (one in the capsule above the head of the fibula and one in the quadriceps tendon above the patella), hand—three (two adjacent to the metacarpophalangeal joint of the fifth finger), wrist—one (distal to the head of the ulna), hip—one (mesial to the trochanter and superior to the joint capsule), elbow—one (in the joint capsule adjacent to the lateral epicondyle), and near the ankle—one (lateral to the external malleolus).

On the other hand, three papers describe localized deposits of calcium in the vicinity of certain specific joints. Milch and Green⁴ report five cases of calcification about the flexor carpi ulnaris tendon and regard this condition as a distinct clinical entity. Mauritz⁵ reported one case of acute intermetacarpophalangeal calcification with redness and swelling of the hand.

Goldenbert and Leventhal⁶ reported five cases of calcified deposits above the trochanter, apparently in the tendon of the gluteus medius muscle, and stated that similar deposits were seen in the roentgenograms of 30 of the hips of 550 patients which they examined. One of these cases was operated upon, and the tissues above the trochanter were found to contain a plaque of bone two inches long by one and one-fourth inches wide. Nilsson⁷ also reported a case of calcification in the gluteus medius tendon in which some true bone formation was present in the tendon in association with the calcium deposits. Sandstrum and Wahlgren⁸ reported 12 cases of calcareous peritendinitis in which the shoulder was involved eight times, the hip twice, the knee once and

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 8, 1948.

the heel once. As will be noted below, we believe that these calcium deposits in various locations are similar to one another and can be grouped together rather than regarded as separate clinical entities.

INCIDENCE

The occurrence of calcium in the region of the shoulder is a relatively frequent condition and one which is often associated with stiff and painful shoulders, periarthritis and tendinitis of the shoulder, or subdeltoid or subacromial bursitis. McLaughlin⁹ states that almost 2,000 lesions which are commonly diagnosed and treated as "calcified subdeltoid bursitis" were studied by the fracture service of the Presbyterian Hospital over a period of 15 years. Dickson and Crosby¹⁰ found that 73, or 36.5 per cent, of 200 cases of periarthritis of the shoulder showed deposits of calcium which were visible in the roentgenograms. In a study of 6,061 unselected adults who were subjected to fluoroscopic examinations, Bosworth¹¹ found calcium deposits in one or both shoulders in 165, or 2.7 per cent. Of 138 such individuals who were company employees and on whom accurate records were available, the deposits were bilateral in 46.4 per cent, thus, calcium was present in 202 shoulders. In these patients, symptoms referable to the shoulder were present at one time or another in 70 shoulders, or 34.6 per cent, while the remainder were quiescent and caused no symptoms during the three-year period of observation.

On the other hand, calcium deposits in the vicinity of joints other than the shoulder are relatively rare, or at least not many such cases have been reported in the literature. During the past 10 years I have encountered 20 patients with deposits of calcium in locations other than in the musculotendinous cuff of the shoulder. These were distributed as follows: coracoid process, 1, elbow, 4, wrist, 3, hand, 4, (all adjacent to a metacarpophalangeal joint), hip, 4, knee, 2, and foot, 2 (adjacent to the second metatarsophalangeal joint and heel). These were all in different patients.

ETIOLOGY

Wells¹² states that calcification seldom occurs in normal tissue except in the formation of bone but that any area of dead tissue that is not infected and that is so large or so situated that it cannot be absorbed, will probably become infiltrated with lime salts. Exceptions to this rule are the metastatic calcification of Virchow, which occurs in individuals in whom the blood is oversaturated because of calcium absorption from the skeleton, and *calcificans universalis*. But in normal individuals it appears that local degeneration of the tissue precedes the deposition of the lime salts.

Determination of the calcium, phosphorus and alkaline-phosphatase content of the blood in several of our patients with local deposits of calcium has failed to reveal anything abnormal, and this has also been the experience of other observers. Consequently we must assume that in these patients with deposits of calcium about joints degeneration of the involved tendon or of the ligament or capsule of the joint preceded the deposition of calcium and that the primary cause of the trouble is the cause of the degeneration.

However, the fact that the deposits are so frequently bilateral in the shoulder (46.4 per cent in Bosworth's larger series) suggests that there may be some constitutional predisposition to the deposition of calcium in the vicinity of joints which is so slight a variation from the normal that we have not yet succeeded in detecting it. Another possibility is that in certain individuals the musculotendinous cuff is predisposed to degeneration, either because of some anomaly in the structure of the shoulder which exposes it to injury or because of inherent weakness of the tendon. Dickson and Crosby believe that deposition of calcium is determined by some underlying alteration in the physical state, which is influenced by foci of infection and by endocrine irregularities.

It has been noted by Codman and others that the onset of symptoms may follow an injury or that the symptoms may begin spontaneously without any known cause. Since we know that silent or asymptomatic calcium deposits are not uncommon, it is probable that the single injury which is alleged to have caused the deposit may have aggravated or produced symptoms in a silent deposit. It is possible that the trauma may injure the tissue surrounding a silent deposit and cause the calcium to spread to tissue where it can cause symptoms. On the other hand, it also seems possible that an injury may have caused the degeneration which laid the foundation for the calcium deposit. Bishop¹⁴ believes that minor traumas may cause rupture of a few fibers of a tendon (supraspinatus) with few or no symptoms and that these may heal but that frequent repetition of the injury may lead to hyaline degeneration and the depositing of calcium in these areas. Bosworth's figures indicate that occupations which involve excessive use of certain muscles, as, for instance, the supraspinatus in typists, may predispose to the formation of calcium deposits in the tendons of their muscles, and that these may appear within two months or less.

The calcium salts are withdrawn from the blood, where they are held by the proteins in an unstable state of suspension or solution. It is believed that the increased alkalinity or decreased carbon dioxide which is present in degenerating or necrotic tissues causes the calcium carbonates and phosphates in the fluids which are seeping through these tissues to be precipitated. Klotz¹⁵ believed that the deposition of the calcium is preceded or accompanied by the formation of soaps in the degenerating tissue and that these withdraw the calcium from the body fluids and that the fatty acids are then replaced by carbonic and phosphoric acids to form more stable carbonates and phosphates of calcium. Wells does not accept the view that the formation of calcium soaps constitutes an essential step in pathologic calcification and states that it is probable that there are no essential differences between this and normal ossification.

PATHOLOGY

In pathologic calcification the calcium phosphates and carbonates are in the same proportion as in the bone. The substance first appears as minute amorphous granules which are scattered irregularly through the degenerating tissue or fibrin matrix. These coalesce to form spherules or larger masses

FIG 1



A

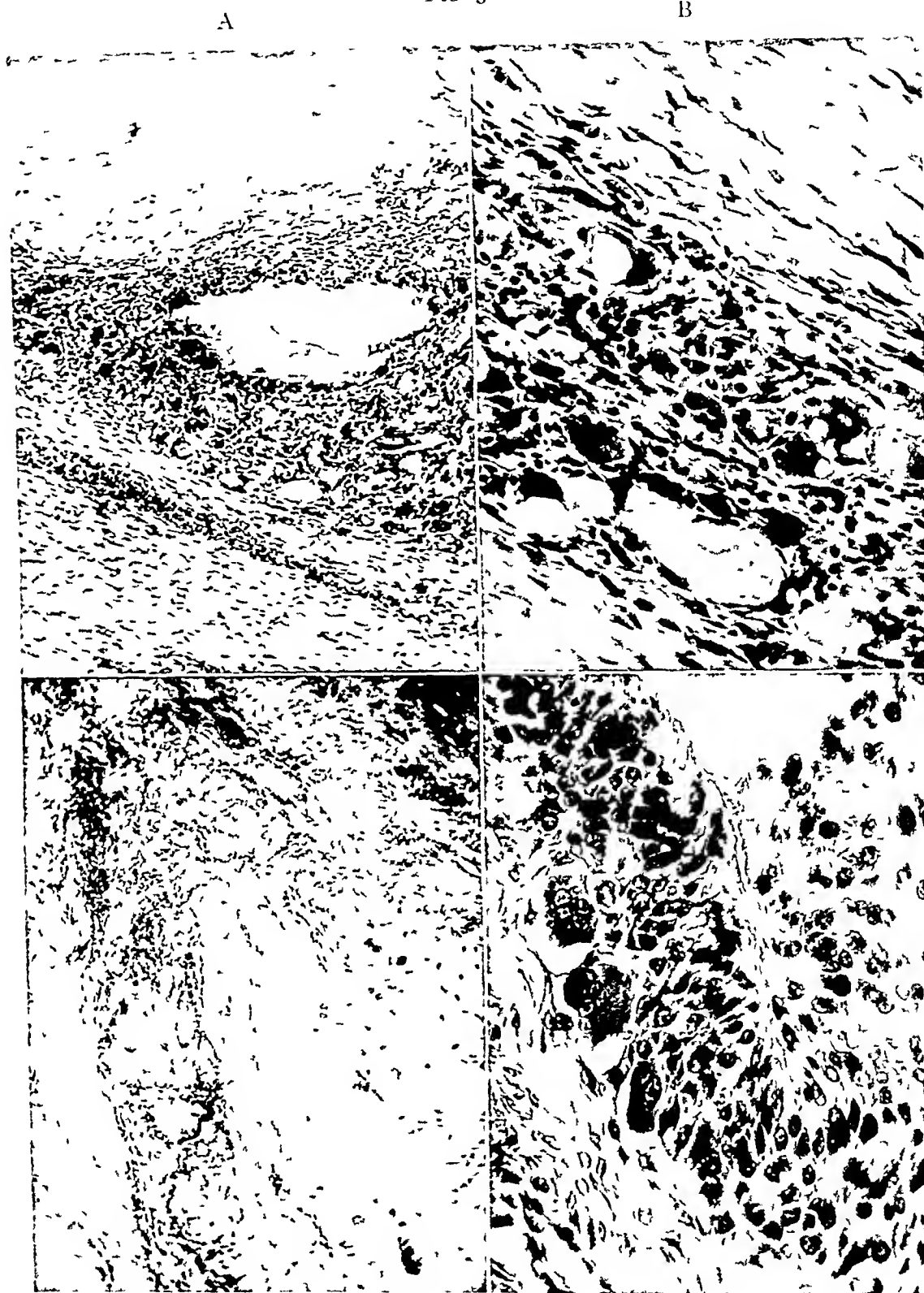
FIG 2

B

FIG 1—(A) Small calcium deposits in fibrous tissue adjacent to the elbow in which the form of the fibers appears to be preserved by the degenerated material $\times 110$ (B) Larger mass of calcium deposit from the same lesion with cellular infiltration of the degenerating tendon $\times 225$

FIG 2—(A) Subacute inflammation with round-cell infiltration in areolar tissue adjacent to the elbow. The artery above and the nerve below and a bit of a calcium deposit are seen in the upper left-hand corner $\times 75$ (B) Artery and round-cell-infiltrated fibrous tissue lying between two large calcium deposits from the same specimen $\times 70$

FIG 3



A

FIG 4

B

FIG 3—(A) Calcium deposit in the supraspinatus tendon with giant cells and round-cell infiltration $\times 70$ (B) Higher-power photomicrograph of a smaller similar deposit in an apparently normal tendon from the same specimen $\times 225$

FIG 4—(A) Large and smaller cystlike areas containing calcium and degenerated tissue debris in a chronic lesion of the supraspinatus tendon $\times 45$ (B) High-power photomicrograph of a portion of the wall of a similar lesion adjacent to the elbow. Note the small giant cells and what appear to be modified fibroblasts lining the cavity $\times 300$

which are scattered through the tissue or mixed with the organic ground substance which is presumably the disintegrating remains of the degenerated tissue, but there is no diffuse infiltration of a living tissue with calcium salts such as occurs in the formation of bone

The gross appearance of the deposit when exposed at operation varies with the location and duration of the deposit as well as with the condition of the surrounding tissue. We have operated upon approximately 50 calcific deposits in the musculotendinous cuff of the shoulder and on nine of the 17 cases which are reported here as having occurred in the vicinity of other joints

In our experience, the calcium deposits in the shoulder vary considerably in size, number and location as well as in the consistency of the calcified material. Bosworth found that 51.5 per cent of the involved shoulders had deposits in the supraspinatus portion of the cuff, 44.5 per cent in the infraspinatus, 23.3 per cent in the teres minor. Only five shoulders showed calcium in the subscapularis and 25 showed calcium in the subacromial bursa. Multiple deposits occurred in 20.3 per cent of the involved shoulders. We have not attempted to record the locations of the deposits in our shoulder cases.

A fairly typical operative finding in an acute case is for the floor of the subdeltoid bursa to present a dome-like swelling about two centimeters in diameter. The apex or center of this furuncle-like swelling is white and this is surrounded by a purplish or red inflammatory zone, which shades off into the slightly inflamed floor of the bursa. When the apex of this swelling is incised, white or yellowish-white material of the consistency of tooth paste exudes on the floor of the bursa. When the remainder of the calcific material is removed with a curette, a cavity is left in the tendon which has a ragged avascular surface, this may be so deep that it appears to extend down through the tendon into the underlying bone.

In some hyperacute cases of short duration, the calcific material is thin or milklike in consistency and may be under such pressure that when the surface of the tendon is incised, the contents of the deposit may spurt into the air. In others the deposit may have ruptured into the bursa and the bursa may be found to be distended with a thin, milklike fluid. In chronic cases, the calcium deposit may be inspissated, and upon incising the tendon the surgeon encounters one or more dry, chalky deposits which can be removed with a curette. There are all gradations between the types of deposit described above.

It is probable that the deposits are nearly always multiple and that the surgeon never sees many of the small deposits which are buried deep in the tendinous floor of the bursa. We have encountered many such minute deposits in microscopic sections of apparently normal tendon from the floor of the bursa. Likewise, the moderately large deposits (0.5 cm. or more in diameter) may exist in the same musculotendinous cuff.

In deposits in areas other than in the musculotendinous cuff of the shoulder, it has been my impression that the calcium was not under tension in the tendon or ligaments but was in a thin-walled cavity or free in the adjacent areolar tissue.

The microscopic picture varies with the state of inflammation in the tissues adjacent to the calcium deposits. Since most of the sections which I have studied were taken from acutely inflamed lesions, I have not been impressed with appearances of degeneration or even with relative avascularity in these tissues. Frequently in tendons the small calcium deposits may be present as spindlelike collections of granular material surrounded by apparently normal tendon fibers. In adjacent areas the fibers may be fragmented and curled or hyalinized or may appear normal.

More frequently than not, the tissue was more vascular and more cellular than normal. In most instances in which the operation was performed for moderately acute pain and disability, the tissue adjacent to the calcium deposit was infiltrated with small and medium-sized round cells (monocytes or epithelioid cells). Some of these cells were present in the necrotic tissue debris which was mixed with the calcium deposits. Small foreign-body giant cells were also present here. In the lesions of longer duration, the giant cells were larger and more numerous. The absence of blood pigment in the tissues and in the macrophages suggests that the lesion had not been the site of a previous hemorrhage and thus was probably not traumatic in origin. In harmony with the accumulation of round cells in the area, there was proliferation of the fibroblasts and an increase in the vascularity in the tissue adjacent to the deposits.

In the hyperacute lesions with severe pain and disability large numbers of polymorphonuclear leukocytes were present in the calcium deposits and in the surrounding tissues and many of these cells were disintegrating. Likewise, in some of the acutely inflamed deposits near joints other than the shoulder, the areolar tissue contained fibrin and this was infiltrated with leukocytes and round cells.

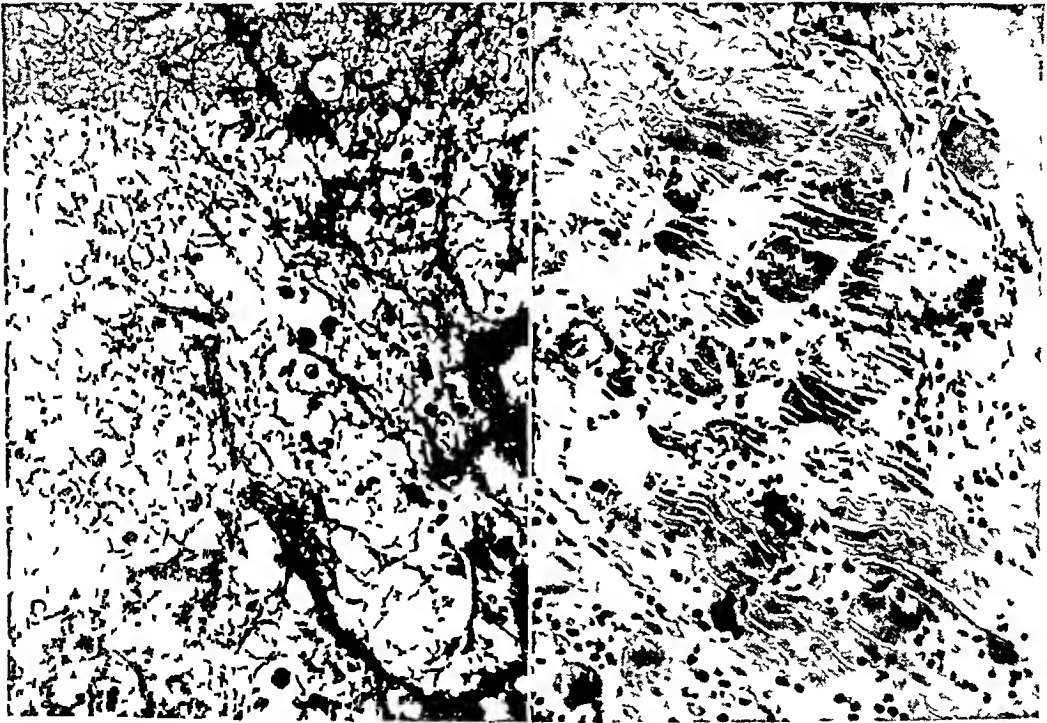
In some of the more chronic cases in the shoulder rather large, cystlike cavities which contained debris and calcium were surrounded by a definite wall of chronic inflammatory tissue. Cultures from these deposits have been sterile and there is no indication that infection plays any part in the process. The inflammation is apparently due to chemical irritation and foreign-body reaction.

In locations other than the musculotendinous cuff of the shoulder, the calcium deposits have been found in the areolar tissue superficial to a tendon or ligament near its attachment to bone or in the musculotendinous origin of muscles near the bone. The deposits may have begun in the dense connective tissue and extended outward but were not found there at operation. Consequently, the dense connective tissue of the tendon is usually absent from the microscopic sections and areolar tissue may be found in the vicinity of the calcium deposits. No other difference was found between the microscopic picture of the lesions in the shoulder and those in the vicinity of other joints.

SYMPTOMS AND CLINICAL COURSE

It is probable that these calcific deposits begin as microscopic precipitates of calcium salts which gradually increase in size until they encroach upon the

surrounding tissues and cause an inflammatory reaction there. Such a calcium deposit may be present in the tissues for months or even years and cause no symptoms and then suddenly, after an injury or without any known precipitating cause, may become the central point of an area of acute inflammation, with severe pain and disability. The reason for this is not known. The inflammation is the cause of the symptoms. Apparently the process is a reversible phenomenon and the calcium may be resorbed either spontaneously or as a result of the inflammatory reaction. Whether these primary deposits are in the cells, between the connective-tissue fibers or in the fibers has not been determined satisfactorily. As they increase in size, the calcium is mixed with debris of degenerating connective-tissue fibers and cells.



A

B

FIG 5—(A) Coagulated fibrin infiltrated with degenerating round cells and leukocytes from a hyperacute lesion mesial to the coracoid. (B) Hyalinization and fragmentation of fibers of the teres minor muscle, with infiltration by leukocytes and round cells in a hyperacute lesion.

It is evident that most, if not all, of these deposits are silent or asymptomatic in the beginning and it is probable that the majority of them slowly attain a moderate size, persist for an indefinite period and then disappear without causing symptoms. In Bosworth's series only 70, or 34.6 per cent of the involved shoulders had been the seat of pain or discomfort either prior to or during the three-year period of observation. He also noted that the larger deposits (1.5 cm or larger in diameter) tended to cause symptoms and that the size of the deposit tended to be in accord with the symptoms, yet one-third of the large deposits in his series gave rise to no complaints during the period of observation. Howorth,¹⁵ however, states that large deposits may be almost

symptomless while small deposits may be associated with considerable pain. He further states that deposits may change in size and density within a few days.

The symptoms are those of local inflammation in the involved area, that is, pain and disability, and these vary greatly in degree and are sometimes classified as hyperacute, acute, subacute, and chronic depending upon the intensity and the duration of the symptoms. In a hyperacute case, the onset may be abrupt with severe throbbing pain in the shoulder which prevents the patient from sleeping or even from resting in bed. The pain may remain sharply localized or may spread up over the side of the neck and behind the shoulder and down the arm to the insertion of the deltoid muscle and even to the fingers. It is aggravated by the slightest movement of the extremity or by pressure over the front of the shoulder or the back of it. Such patients may require opiates for relief of the pain.

In the average acute case, the pain is less gradually, sometimes following a direct blow or unusual strain or posture, coming on the shoulder, but usually without a preceding trauma. It may be a low grade ache or a period on several days until the patient is troubled by a more constant dull ache in the shoulder which is aggravated by movement or by pressure or the application of local heat. Unless the condition subsides or is relieved by treatment, the pain tends to spread up over the side of the neck and down the scapula and it centers especially at the insertion of the deltoid muscle and may extend down to the fingers. As in many other conditions, the pain is worse at night.

The patient tends to hold the arm next to the side with the forearm supported across the chest. His posture is such that the condition resembles that described as the soldier's syndrome, but it is suggested that the referred pains are due to reflex spasm of the scapulo-humeral vessels. With the passage of time, the movements of the shoulder, especially upward or external rotation and abduction become progressively restricted and the muscles of the shoulder become atrophied. At first the limitation is due to muscle spasm, but later structural changes occur in the capsule and periosteal tissues and fix the humerus to the scapula, and the atrophy involves not only the muscles but also the bones and especially the greater tuberosity of the humerus. This severe painful disabling condition may continue for months or may subside spontaneously at any time.

Many patients never have severe pain or disability but complain of occasional painful catches in the shoulder with certain movements, especially abduction or rotation, and of inability to sleep on the affected side. These subacute symptoms may persist or recur at intervals over periods of months or years.

The findings on physical examination vary with the symptoms. In a patient with hyperacute symptoms the arm is held close to the side and the forearm may be supported across the chest. There may be slight swelling of the front of the shoulder, and the area over the anterior surface of the greater tuberosity of the humerus is quite tender and an exquisitely tender point can be localized. The patient objects to attempts to move the arm in any direction, but usually a moderate amount of forward flexion can be carried out passively without

causing much pain. There may be a moderate increase in temperature and the white blood-cell count may be moderately elevated.

In the average acute case of short duration, the appearance of the shoulder is normal. Palpation reveals a small area of acute, sharply localized tenderness over the anterior surface of the greater tuberosity of the humerus just below the anterior margin of the acromion. This point of tenderness may be located mesially over the tendon of the long head of the biceps or laterally over the infraspinatus tendon. The tenderness is most marked directly over the calcium deposit and if this is in the tendon of the *teres minor*, the point of maximum tenderness is more distal and more lateral on the shoulder. The arm is held at the side and the patient does not object to a moderate amount of manipulation, but the range of movement in rotation or abduction is moderately limited and causes pain, while movement in flexion or extension is fairly free and painless.

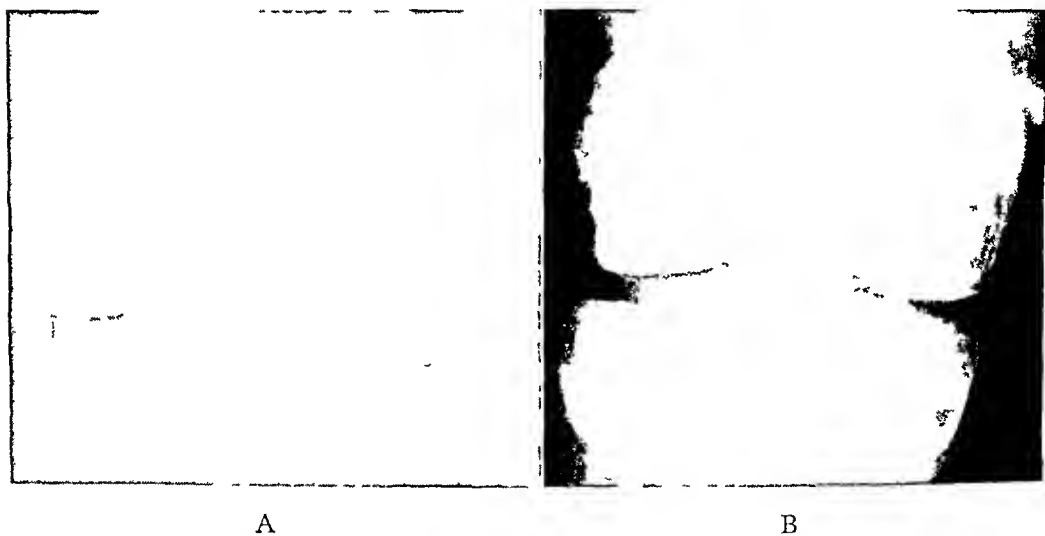


FIG 6—(A) Knee joint with a calcium deposit adjacent to the intercondyle of the femur. This produced severe pain and disability and was operated upon early, with complete relief. (B) Calcium deposit adjacent to the intercondyle of the femur. This failed to yield to conservative treatment over a period of three and one-half months and was operated upon, with complete relief of symptoms.

In cases with severe symptoms and of longer duration, the pain and tenderness involve a wider area, and there may be tenderness on deep pressure over the side of the neck (*scalenus anticus* muscle and the cords of the brachial plexus), over the superior angle of the scapula and over the insertion of the deltoid. The atrophy of the muscles of the shoulder is evident on inspection and palpation and if the scapula is fixed and the arm manipulated it will be found that there is very little scapulohumeral movement and that movement of the extremity is accomplished by movements of the scapula on the thorax.

The subacute case may present nothing on physical examination except an area of moderate tenderness over the front of the tuberosity and a painful catch with certain movements of the arm. Usually the catch is felt when the arm is lowered actively to the side from a position of abduction and external

rotation. It seems to be produced by the painful area sliding under the margin of the coraco-acromial ligament.

The calcific deposits in the vicinity of other joints produce local pain and disability, which vary in intensity from time to time and in different cases just as occurs in the shoulder. For instance, the small calcium deposit over the internal lateral ligament of the knee shown in Figure 6(a) had caused symptoms for only three days, but the pain was so severe that the patient was confined to bed and maintained the knee in a position of acute flexion, and he complained bitterly when an attempt was made to straighten the extremity or when pressure was made over the painful area. He was operated upon one Sunday afternoon as an emergency case in order to relieve the intense pain. The other quite similar deposit in this area shown in Figure 6(b), occurred in a large, active woman. It interfered very little with the patient's activities and was observed and treated conservatively over a period of more than three months and finally was operated upon because of persistent annoying pain and tenderness.

Of the other deposits not in the musculotendinous cuff which I have operated upon, the two at the shoulder (one in the teres-minor muscle posterior to the humerus and one mesial to the tip of the coracoid) were operated upon to relieve severe acute pain of short duration. The others (three at the elbow, one at the wrist and one in the hand) were operated upon on account of persistent mild pain, tenderness and disability which did not subside under conservative treatment.

One of the cases of a deposit adjacent to the flexor carpi ulnaris tendon reported by Milch and Green was of the hyperacute type, with swelling of the wrist and red streaks extending up the arm resembling lymphangitis. Likewise, the case at the metacarpophalangeal joint reported by Mauritz presented considerable swelling of the hand. Such very acute cases may exhibit a moderate elevation of temperature and of the leucocyte count. In the usual case however there is no swelling or redness, the pain is moderate in degree and is produced by local pressure, or movements which cause tension or increased pressure in the involved area, and there are no general symptoms.

THE ROENTGEN FINDINGS

The presence of a localized deposit of calcium in the tissues may be suspected, but the diagnosis is not made unless the material can be visualized in the roentgenogram. From what has been written above, it is evident that the deposits vary considerably in size and density. Many small ones will not cast a shadow and cannot be seen with the fluoroscope or in the roentgenogram. Consequently, these cannot be diagnosed clinically. Larger deposits may be obscured by overlying bone. This is especially true of the musculotendinous cuff of the shoulder, where the calcium may be spread out in a thin layer and may not cast a shadow dense enough to be seen through the bone or even through thick soft tissue, unless it is seen in profile.

Bosworth advises that the shoulder be examined under a fluoroscope while the arm is carried through the full range of movement. Then if calcium

deposits become visible, spot films are made in order to visualize them more clearly and record their position. However, most calcium deposits in the musculotendinous cuff of the shoulder will be seen in a film taken with the arm at the side and in a position of external rotation. We routinely have a second anteroposterior exposure made with the arm rotated inward, and occasionally a third inferior-superior or vertical view with the film on top of the shoulder.

In joints other than the shoulder the calcium can be shown roentgenographically with less difficulty and is usually visible in the routine films taken in two planes. It tends to vary in density with the duration of the symptoms, the image being more dense in instances in which the symptoms have been present for a longer time. The margins of the deposit tend to be poorly defined on the roentgenogram and the density may be irregular. It can usually be differentiated from bone by the fact that it shows no evidence of internal structure.



FIG 7—Wrist joint with faintly visible calcium deposit distal to the styloid of the ulna. This cleared up promptly after deep roentgenotherapy.

TREATMENT

The treatment of calcium deposits varies with the severity of the symptoms and with the tolerance of the patient for the symptoms. If the deposit is discovered accidentally and is causing no symptoms, no treatment is indicated. If the deposit is causing sufficient pain and disability to lead the patient to consult a physician for relief, then treatment is indicated and this may either be conservative or radical measures may be instituted.

Conservative treatment is largely palliative. Its success is based on the fact that in practically all these cases the pain will subside if the patient can wait long enough, and in most instances function will be restored to the part. It is probable that the inflammatory reaction which causes the symptoms also results in an increased vascularity in the area and that this tends to promote resorption of the deposit. For this reason, the hyperacute symptoms rarely last very long. However, though these symptoms may lessen to a point where they are tolerable, they may still be the cause of much pain and disability and may result in chronic stiff and painful shoulders persisting for many months or even years. It is questionable whether or not any form of conservative treatment actually influences the course of the disease or causes resorption of the deposit.

The conservative measures in use are local heat, local cold, immobilization, exercises, sedatives and deep roentgen therapy.

Local heat may be applied as moist heat from hot compresses, or dry heat

tion from an electric pad, hot-water bag, infrared lamp or diathermy. If the symptoms are severe, heat may aggravate the pain. In many cases, however, heat has a soothing effect and it may enable the patient to sleep. Some surgeons believe that diathermy may actually promote the resorption of the deposit. I have not seen this occur and believe that long-continued diathermy may be harmful.

Local applications of cold, as cold compresses or an ice bag, may give considerable relief to patients with severe pain.

Immobilization of the part in a sling or bandage or by strapping or even by a plaster of Paris splint or cast may afford some relief but should be avoided with lesions in the shoulder as it encourages stiffness of this joint which may be difficult to overcome.

Exercises are useful in restoring function to the part after the acute symptoms have subsided. They are especially helpful in chronic lesions of the shoulder. Passive stretching by continued traction is used in some cases with frozen shoulders. As much sedation as is necessary is given while the traction is acting.

Sedatives are used as indicated for pain. Salicylates and codeine are useful, either alone or in combination, and we give the patients large doses of vitamin B.

Deep roentgenotherapy has been used quite extensively during recent years and there are reports in the literature in which it is recommended as an almost infallible cure for calcium deposits in the musculotendinous cuff of the shoulder. I have advised it for a considerable number of patients during recent years but am still not in a position to make a statement concerning its efficiency. In some mild or moderately severe cases deep roentgen treatment has seemed to afford some relief while in others it has had no apparent effect. In hyperacute cases with severe pain, it has not appeared to do any good. The same is true of chronic cases, and especially when there are severe capsular adhesions or contractures. In the latter the roentgenologist should restrain his enthusiasm or burns may be the result.

The more radical methods of treatment are manipulation under general anesthesia, needling with or without irrigation and operative exposure and removal of the deposit.

Manipulation under general anesthesia is used in breaking up the adhesions and restoring movement to shoulders with marked limitation of motion. After the patient is relaxed by the anesthetic, the arm is abducted fully and then rotated externally and internally while the scapula is fixed to the chest by an assistant. It is desirable that the arm be carried through the complete range of movement. If a calcium deposit is present, the manipulation should be combined with open operation for removal of the deposit. The manipulation is not without danger, as the anterior and inferior portions of the capsule are usually torn if the limitation of motion is marked, and the shoulder may be dislocated or the humerus may be fractured. After the manipulation, the pain may become aggravated and the adhesions may recur unless this is prevented by stretching and exercise. During the first few days, the patient is kept in bed.

with the arm in abduction and external rotation (The wrist is tied to the head of the bed)

Needling of the deposit is a procedure which was quite popular a few years ago and is still used in some clinics. It is most useful in an acute case with a single relatively large deposit. Under local or general anesthesia a relatively large (18- or 16-gauge) needle is introduced into the deposit and as much as possible of the calcium-containing material is aspirated. Then multiple punctures are made in the area in order to produce inflammation and stimulate

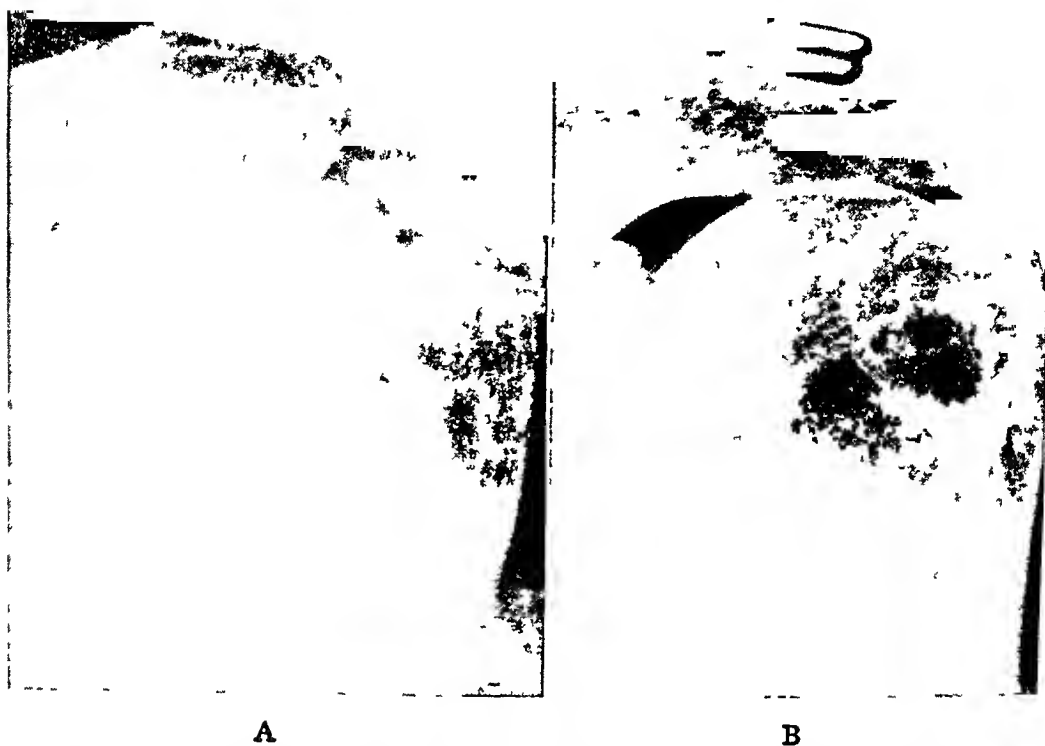


FIG 8—(A) Unusually large calcium deposit in the musculotendinous cuff of the shoulder. The duration of symptoms was about two and one-half years, with several acute episodes. (B) A view of the same shoulder, as shown in Figure 8A immediately after operation, shows that a considerable amount of calcium was missed and left in the shoulder, but the patient was relieved of her symptoms by the operation. It is believed that the remaining calcium will disappear gradually.

absorption of the remainder of the calcium. In the shoulder this may be combined with irrigation of the subdeltoid bursa either with or without a second needle in the bursa. In my hands, needling is done under local anesthesia and is used for those patients when operative removal of the deposit is indicated but who do not wish to be operated upon. It is apt to be followed by a few days of severe pain and is not as reliable a form of treatment as is the operative removal of the deposit.

Operative removal of the deposit is the surest method of affording the patient prompt and permanent relief. It is especially indicated in patients with severe pain and multiple deposits or with one small deposit which is difficult to enter with a needle or in patients who have failed to obtain relief after a needling procedure.

OPERATIVE TECHNIC

If the deposit is in the shoulder, the operation may be performed under local or general anesthesia, with the patient supine on an ordinary operating table or in the sitting position, preferably in a dental chair with a support for the head. Abbott¹⁶ recommends local anesthesia and the sitting position because the arm can be moved actively by the patient and the areas of tenderness can be more accurately localized after the bursa is opened. This is especially true of those deposits which lie deep in the tendon and cannot be seen on inspection.

The point of maximum tenderness should be noted before the operation and the incision should be made directly over this point. The incision begins over the margin of the acromion and extends downward for about two inches over the point of maximum tenderness. The deltoid fibers are split to expose the wall of the bursa and this is incised, or a window about one inch square may be removed to expose the musculotendinous cuff which forms the floor of the bursa. The calcium deposit which is causing the trouble is usually visible as an elevated inflamed area with a white or yellowish center. This is incised in line with the fibers of the tendon, the contents are allowed to escape and a specimen of the wall of the cavity is removed.

The cavity containing the calcium is then scraped lightly with a curette, but no attempt is made to remove all the calcium, as this infiltrates the surrounding tendon and its removal would entail extensive damage to the tendon and do more harm than good. It is probable that merely incising and draining the deposit is all that is necessary for a cure, as this will lead to resorption of the remainder of the calcium.

The shoulder is then rotated inward and outward to expose more of the floor of the bursa, and any other suspicious areas in the tendon are incised in a similar manner. If calcium deposits are found, the larger ones are curetted lightly while the smaller ones are simply drained by the incisions. These multiple, short incisions parallel with the tendon fibers are not sutured and seem to heal without disability. They may reveal deposits which would not have been seen otherwise. Also it is evident that in many shoulders there are deposits which are not drained by the operation, as the surgeon must avoid doing any more harm than necessary.

In some cases, no deposit or elevation of the floor of the bursa is visible and in such instances one or more parallel incisions are made through the tendon until the deposit which is being sought is entered and its contents are then evacuated. The surgeon should endeavor to evacuate all large deposits and especially those that are causing the symptoms.

After the larger calcium deposits have been incised and evacuated, the surgeon manipulates the shoulder into full abduction and internal and external rotation in order to break up adhesions which may have formed. This is especially important in cases of long duration, with limitation of movement due to structural changes, and may require a small amount of pentothal or

other general anesthetic if the operation is being performed under local anesthesia

The wound is then closed in layers and covered with a small gauze dressing

POSTOPERATIVE TREATMENT

In the acute cases, no immobilization is necessary and the patients may leave the hospital a day or two after the operation and return for removal of the sutures on the sixth postoperative day. They are encouraged to use and exercise the arm, and usually the normal range of movement is obtained within a few weeks.

In the chronic cases with adhesions and which have been manipulated, it is advisable to immobilize the arm in abduction and external rotation for a few days after the operation. This can be accomplished by tying the wrist to the head of the bed. The arm is then lowered and pendulum and abduction exercises are prescribed, these may be combined with some passive stretching. The treatment may be continued until a satisfactory result is obtained, which may require several weeks.

Deposits about other joints are treated in the same way as those in the shoulder, that is, conservatively or operatively, depending upon the severity of the symptoms and the wishes of the patient and surgeon. At operation, the deposit is approached by the most direct route, it is incised and curetted lightly and the wound is then closed. They require no special postoperative treatment. The nine patients on whom I have operated in this manner have been relieved of their pain promptly and the condition has not recurred.

PROGNOSIS

As was stated above, the deposition of calcium in the tissues is a reversible process and the calcium may be resorbed spontaneously without causing symptoms or after causing variable amount of pain and disability. It is believed that the inflammation which gives rise to the symptoms causes an increased blood supply in the area and that this hastens the resorption of the calcium. Consequently the very acute symptoms rarely last very long.

In some cases the symptoms subside completely and in others a variable amount of pain and disability remains which may persist for many months.

In severe cases, needling or operative removal of the deposit is often the treatment of choice, the latter usually results in a fairly prompt relief of pain and restoration of function to the extremity. In cases of long standing, this may require several weeks, occasionally a large deposit is discovered after the operation and a second operation may be indicated for its removal. This occurred in one of my patients in whom a deposit was discovered in the teres minor muscle about three and one-half months after the removal of three large deposits from the tendon of the supraspinatus. Since this deposit could not be seen in the original roentgenogram, it is believed that it was a recurrence of the trouble.

On the other hand, one or more rather large deposits may be missed at the time of operation. This occurred in the case illustrated in Figure 9. This

patient was relieved by the operation and it is believed that the calcium which was left will be resorbed as a result of the trauma incident to the operation

SUMMARY

It is noted that localized deposits of calcium occur most often in the musculotendinous cuff of the shoulder but may occur in the vicinity of other joints. The deposits which occur near other joints are similar to those in the shoulder and may be grouped with them.

The etiology, pathology, clinical course, treatment and prognosis of the condition are described.

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DISCUSSION—DR FRANK D. DICKSON, Kansas City, Missouri: I should like to add one area in which calcareous deposits occur which Albert Key has not mentioned in his widespread coverage of the body, that is in the tendon of the long head of the triceps muscle. Deposits in the tendon of the long head of the triceps muscle were observed in two ball pitchers who came under my observation, both fast ball pitchers. I think George Bennett will bear me out when I say that fast ball pitchers almost always have shoulder difficulties from degenerative changes, while curved ball pitchers have trouble in the elbow joint. The difference in the distribution of the pathology is due to the different manner in which the ball is delivered in these two styles of pitching.

One young man belonged to an important baseball team, pitched one game, and was out for the remainder of the season. Examination revealed calcareous deposit in the tendon of the long head of the triceps muscle and a pair of very badly infected tonsils. He was otherwise a very healthy and robust young man, 22 years of age. The tonsils were removed at once, pitching was forbidden, and wheat-germ oil (which I believe contains some form of vitamin C which promotes the absorption of calcium deposits) was administered in full doses. The course of the condition has been followed for three months, and over this period of time the deposits have just about disappeared, and pitching motions can be carried out without pain or discomfort, so it is our opinion that this boy will be able to resume his pitching activities in the spring. The infected tonsils were mentioned because it is my opinion that focal infection does play an important part in formation of these calcareous deposits which are found almost as frequently in women as in men, and in most cases some form of focal infection, usually dental infection, can be unearthed. I must, then, disagree with Doctor Key as to the part played by infection in the formation of calcareous deposits in certain areas of the body, admitting that trauma or wear and tear is usually a factor.

Calcareous deposits in bursae or tendons are incapacitating and usually quite important to the affected individual because of the pain and disability which they produce. It has later been necessary in our experience, however, to resort to surgery. Usually needling of the area or at times irrigation of the area through two good-sized cannulae clears up the situation. If these deposits are irrigated, they usually absorb, probably because of the increased vascularity which follows.

DR EDGAR L GILCREEST, San Francisco. Doctor Key covered so much ground that he did not have time to mention a group of lesions of the shoulder that are extra-articular rather than intra-articular, and which are very disabling. We shall forever be indebted to a great anatomist, A W Meyer of Stanford, for calling our attention to these lesions in a series of articles in the Archives of Surgery a number of years ago. These lesions should be always held in mind when examining a patient past middle life who has a painful shoulder.

The essayist spoke of conservative treatment and also of surgical intervention. Perhaps we should define these two methods more accurately. By the former is meant, of course, rest and heat to the shoulder, by the latter, an open operation. The point I wish to make is that there is a middle ground between the two, that is, aspirating and needling the bursa. This will often give immediate relief to a patient whose pain has been so intense that he has been unable to sleep for several nights.

Time also did not permit Doctor Key to mention the importance of recovering the function of the shoulder as soon as possible by not permitting contracture of the adductor muscles. These shoulders should be held, so far as possible, in a position of abduction and external rotation. We all see frozen shoulders constantly, due to the fact that this fundamental principle was overlooked by the attending physician or surgeon who has been caring for these patients for weeks or months and, as a result, complete function can never be fully recovered.

I enjoyed Doctor Key's paper very much, as it was most interesting.

DR GEORGE E BENNETT, Baltimore. One location that I think it would be well for Doctor Key to look over is the junction of the sacrum and the coccyx. I have seen one or two patients who had to be operated on for removal of the deposit at the articulation of the coccyx and the sacrum. Doctor Johnson and I have seen, within the past year, three or four cases of deposits in the biceps, all of which cleared up with conservative treatment.

DR MURRAY M COPELAND, Washington. I have asked (with his acquiescence) to discuss Doctor Key's paper without comment from him about what I have to say, inas-

CALCIUM DEPOSITS IN VICINITY OF SHOULDER

much as I wish to refrain from stimulating Doctor Key into action with his rapier-like verbal thrusts

I should like to discuss briefly the use of x-ray therapy in some of the calcified lesions described in Doctor Key's able presentation. There is no great mystery about the use of ionizing radiation. It has been found that x-rays, gamma rays and beta radiation may produce direct nuclear effects in atoms of tissue by collisions. Further, indirect ionizing effects are noted through the ionization of water which makes up a considerable portion of body fluids and tissue. Oxidizing agents and reducing agents are formed in the ionization of water, which may alter the pH of body fluids, the respiration of cells and reduce thrombin, *etc*. With these effects it is not difficult to suggest the possible changes in physiology which occur, including dilation of blood vessels, increased tissue fluid exchange of the part irradiated and, frequently, the resorption of excess salts such as calcium, when present. Increased fibrosis, sclerotic vessels, infection or tissue damage, may retard or prevent favorable therapeutic irradiation effects.

I am not offering these remarks as the ultimate explanation, but I think probably the effects mentioned represent some of the biologic changes brought about by ionizing radiations.

DR J ALBERT KEY, St Louis (closing) I do not like to needle shoulders. You have to get the needle in the calcium in the floor of the bursa, and this may be difficult. When it is in the bursa it means the deposit has ruptured and the contents have become disseminated and pressure has been released. Usually those cases get well promptly if you leave them alone. If you can hit the right area with the needle—usually about a 16 gauge, which is quite a needle—and you jam it around in the area, you may get absorption. My experience has been that those people have a pretty tough time for 48 hours and maybe longer after the needling, before they start to get well, while with a little incision which can be made under local anesthesia, one can clean it out and close up, and when the patient wakes up his pain has gone and he gets well.

PARTIAL HEPATECTOMY WITH INTRAHEPATIC CHOLANGIOJEJUNOSTOMY*

A USEFUL ADDITION TO TECHNICAL METHODS FOR THE
MANAGEMENT OF COMMON DUCT STRICTURE

HARWELL WILSON, M D , AND C E GILLESPIE, M D

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF TENNESSEE

ONE OF THE MOST DIFFICULT PROBLEMS encountered by the experienced surgeon concerns the repair of a stricture of the common bile duct. Intrahepatic cholangiojejunostomy with partial hepatectomy, a procedure recently introduced by Longmire,⁵ is a valuable technic for use in certain unusual and especially difficult types of biliary stricture.

ETIOLOGY AND PREVENTION OF BENIGN STRICTURE OF THE COMMON BILE DUCT

It is well known that benign stricture of the common bile duct may rarely occur as a result of infection in and about the duct. Fibrosis of the ampulla of Vater may result in stricture. The majority of benign strictures of the common duct result from injury to the duct acquired during the course of cholecystectomy. Such injuries are most likely to occur when clamps or sutures are placed blindly in an attempt to control bleeding which may take place during a routine cholecystectomy. Experienced surgeons have repeatedly called attention to the necessity for great care in the management of such problems in order that serious complications may be avoided. The surgeon or first assistant can almost always control such hemorrhage by compression of the hepatic artery between the index finger and thumb after the finger has been inserted into the foramen of Winslow. Adequate light, good retraction and proper anesthesia are, of course, necessary before such a situation can be managed safely.

A number of injuries of the common bile duct have occurred in operations that were considered by the original operator to be technically easy. In such instances, the common duct is usually pulled up, ligated and divided without the knowledge of the operator. Adequate surgical training and constant attention on the part of the surgeon are necessary to decrease the incidence of this distressing complication.

METHODS PREVIOUSLY USED FOR THE REPAIR OF COMMON BILE DUCT STRICTURES

The fact that so many methods of repair have been devised for stricture of the common duct is good evidence that no one method is uniformly successful. It is also true that no one method is applicable to all cases. The methods in use have consisted of variations of two general principles. These are (1) end-to-end suture of the duct and (2) suture of the proximal end of the duct to the

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 8, 1948.

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stomach, duodenum or jejunum. Advances have been made in this field, but the problem will long remain a serious one. It is generally agreed that a mucosa-to-mucosa, end-to-end anastomosis of the common duct is the procedure of choice where this can be accomplished. Cattell¹ has been able to accomplish repair by this method in a remarkably high percentage of cases by mobilizing the portion of the distal common duct which lies in a retroduodenal intrapancreatic position. Allen,² by popularizing the Roux Y procedure made

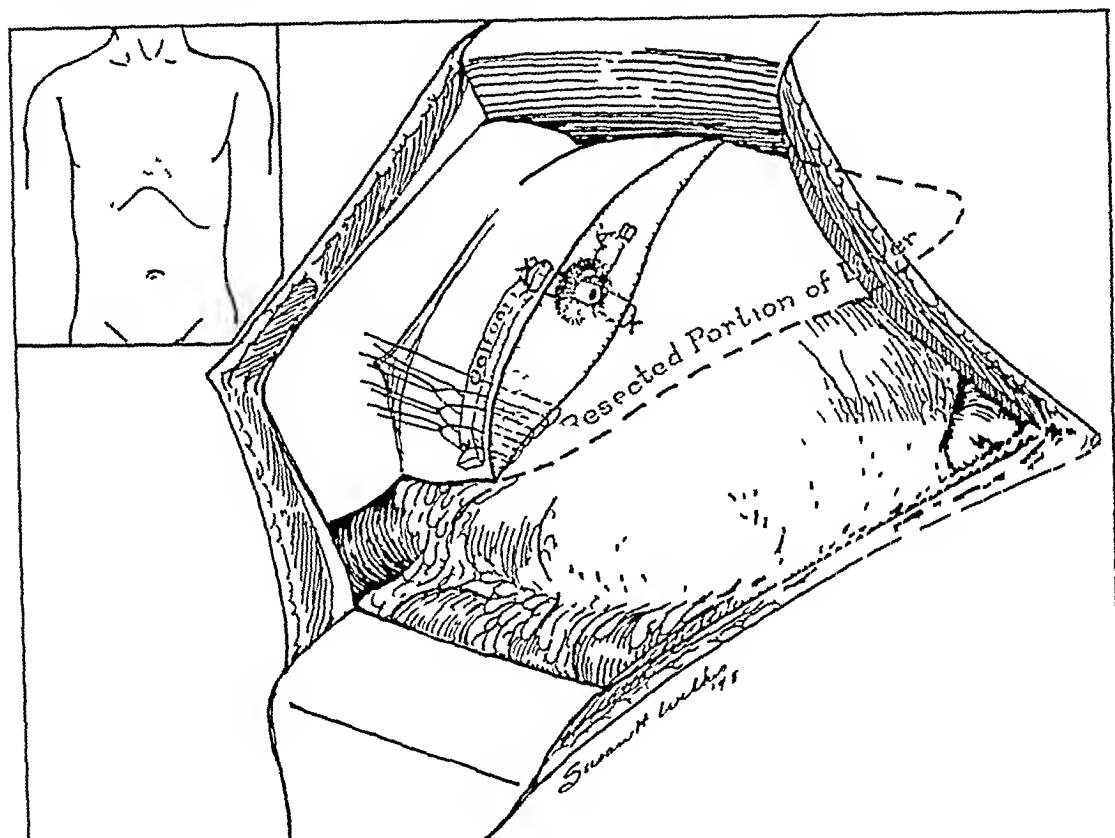


FIG 1 — Resection of left lobe of liver. Bleeding from the cut liver edge is controlled by utilizing overlapping mattress sutures which are tied over a strip of gelfoam. At the site of the intrahepatic duct one mattress suture is placed through the liver substance above the duct and another is placed through the liver below the duct to avoid inclusion of the duct by mattress suture. An artery (A) which requires individual ligation often accompanies the intrahepatic duct (B). A small amount of liver tissue adjacent to the duct is removed with a curette.

Inset shows incision used. Left lobe of liver is delivered into wound after dividing the triangular ligament.

a definite contribution to the problem. Dragstedt³ and Zenninger⁴ have also made helpful suggestions in the management of such cases.

In an occasional case which has resulted from injury or infection, almost no remnant of the common bile duct may be found. It is in such cases that intrahepatic cholangiojejunostomy with partial hepatectomy may offer the possibility of cure in an otherwise hopeless case.

LONGMIRE PROCEDURE

As a result of studies on human livers obtained at autopsy, Longmire concluded that the left main hepatic duct drains the left lobe of the liver, the

quadrate lobe and most of the caudate lobe. Evidence was also found which suggested that the right and left duct systems might communicate through numerous fine ducts in the caudate lobe. Before the Society of University Surgeons in January, 1948, Longmire reported upon a patient in whom he had successfully performed an anastomosis between the main left hepatic duct and the jejunum after performing a partial hepatectomy to expose the duct. It was pointed out that the dilatation produced by chronic obstruction affords a larger duct for anastomosis than otherwise would be found.

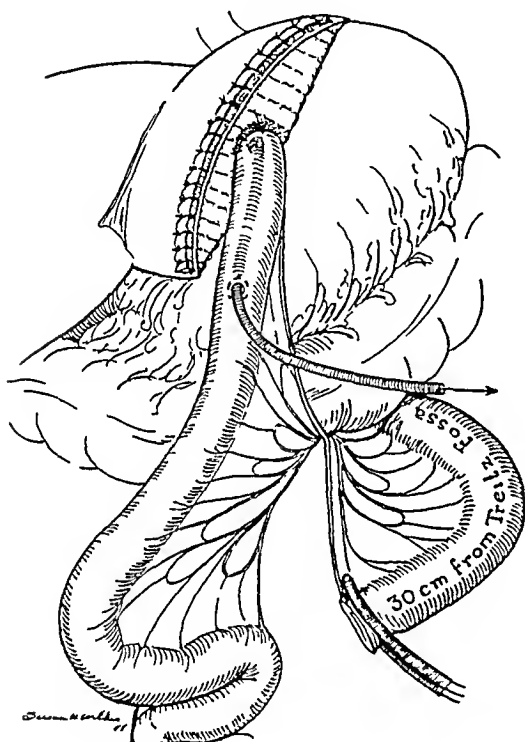


FIG 2—The Roux Y is utilized in securing an end-to-end anastomosis between intrahepatic duct and jejunum. The anastomosis is performed around a catheter which is brought out the jejunum by the Witzel method. Interrupted sutures are used in performing the mucosa-to-mucosa, end-to-end anastomosis. The end of the jejunal loop is partially closed on either side prior to performing the anastomosis in order to compensate for the disparity in size of structures to be united.

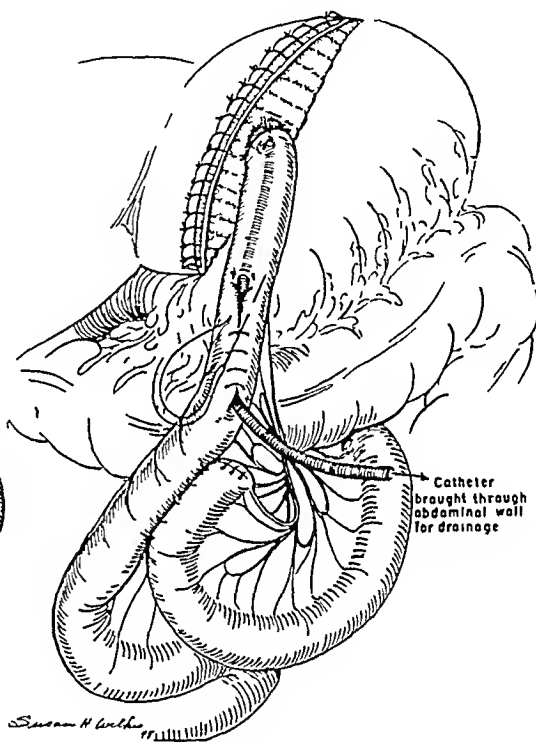


FIG 3—After completion of the duct anastomosis the Roux Y is completed and the catheter is brought outside through a stab wound. Penrose drains are also brought out through stab wound.

Case Report D M, a 44-year-old white male, entered the hospital on our service January 31, 1948. The patient's chief complaint was jaundice accompanied by recurring bouts of chills and fever.

Sixteen months prior to the time we saw the patient he had undergone cholecystectomy. The gallbladder was said to have contained many stones. The postoperative course was uneventful except for an unusually profuse drainage of bile from the wound for a number of days. Subsequent to his original operation the patient began to experience recurrent attacks of jaundice which varied in intensity. He was hospitalized on three

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occasions because of this complaint. On March 21, 1947, the patient underwent an exploratory laparotomy and was told that no obstruction was found in the bile ducts. His condition was not improved by this operation.

The jaundice varied somewhat in intensity but never disappeared. Fever recurred at irregular intervals. The stools were clay colored and there were varied digestive complaints. The patient lost 40 pounds in weight and was forced to give up his work. Physical examination on admission to our service revealed a debilitated white male who was obviously jaundiced. There was a healed upper right rectus scar. Slight tenderness was noted beneath the right costal margin.

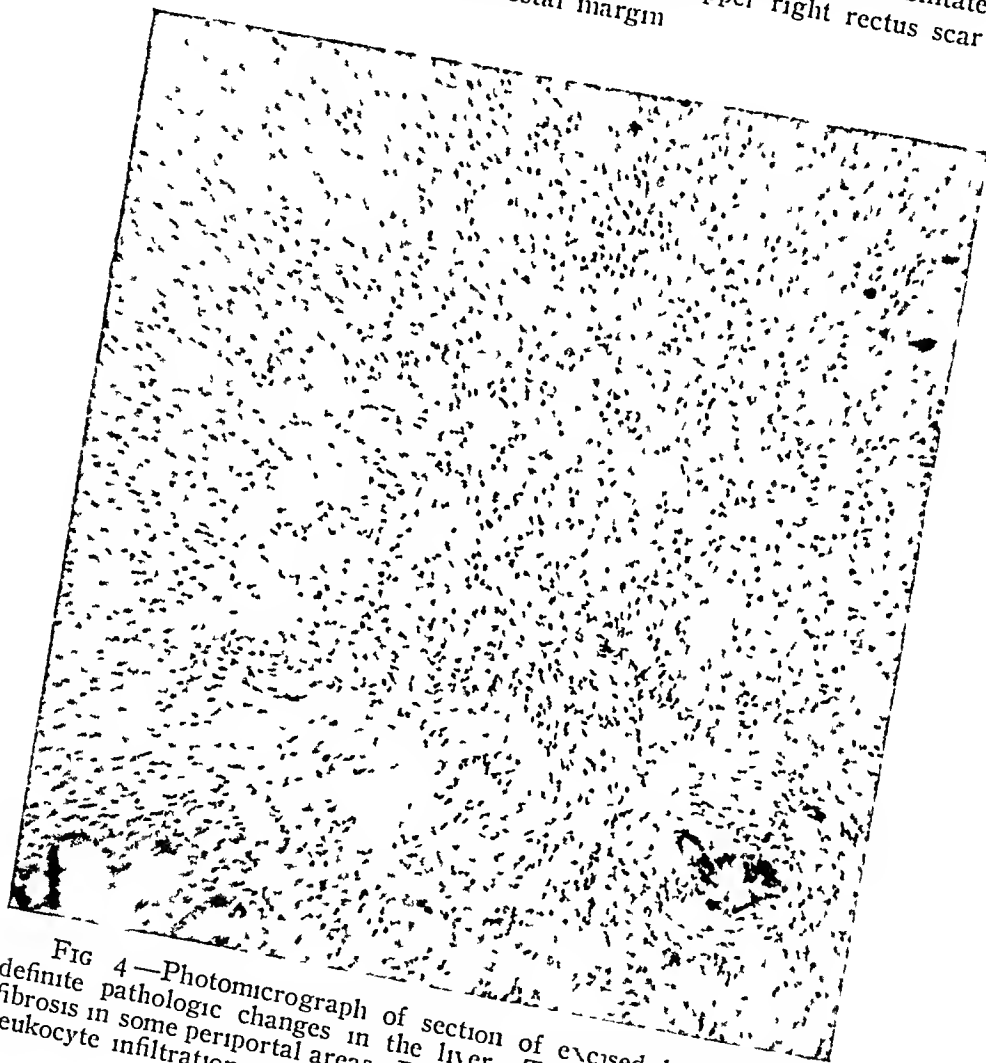


FIG 4—Photomicrograph of section of excised liver reveals definite pathologic changes in the liver. There is a pronounced fibrosis in some periportal areas. Round cell and polymorphonuclear leukocyte infiltration indicate presence of hepatitis.

Laboratory studies revealed the presence of bile in the urine and the absence of bile in the stools. The serum bilirubin at this time was 3 mg per cent and the Van den Bergh reaction was reported as positive direct. The prothrombin time was 20 seconds as compared with a normal control of 40 seconds.

On February 3, 1948, an exploratory laparotomy was done by one of us (C E G). After long and careful dissection with division of many dense adhesions, a diligent search failed to disclose any evidence of a common bile duct, except for a short distal segment which was located behind the duodenum. Three small irregular stones were found in this duct remnant. At the hilus of the liver a small duct approximately 3 mm in diameter and 2 mm in length was found making its exit from the liver substance. A small amount

of bile drained from the duct, but we were unable to catheterize this structure. It was decided to perform a hepatoduodenostomy. Accordingly, a small longitudinal incision was made in the superior wall of the duodenum, which had previously been freed by incising the peritoneum along its lateral border. The duodenum was then lifted and the margins of its opening in the superior wall were sutured to the undersurface of the hilus of the liver. This was sutured about the point of exit of the duct from the liver to give the effect of a sort of cup-like container beneath the duct opening.

The patient was not improved by the procedure. The jaundice persisted, as did the recurring attacks of chills and fever. It was our opinion that the Longmire procedure, namely, partial hepatectomy and anastomosis of the bile duct of the left lobe of the liver to the jejunum, was indicated.

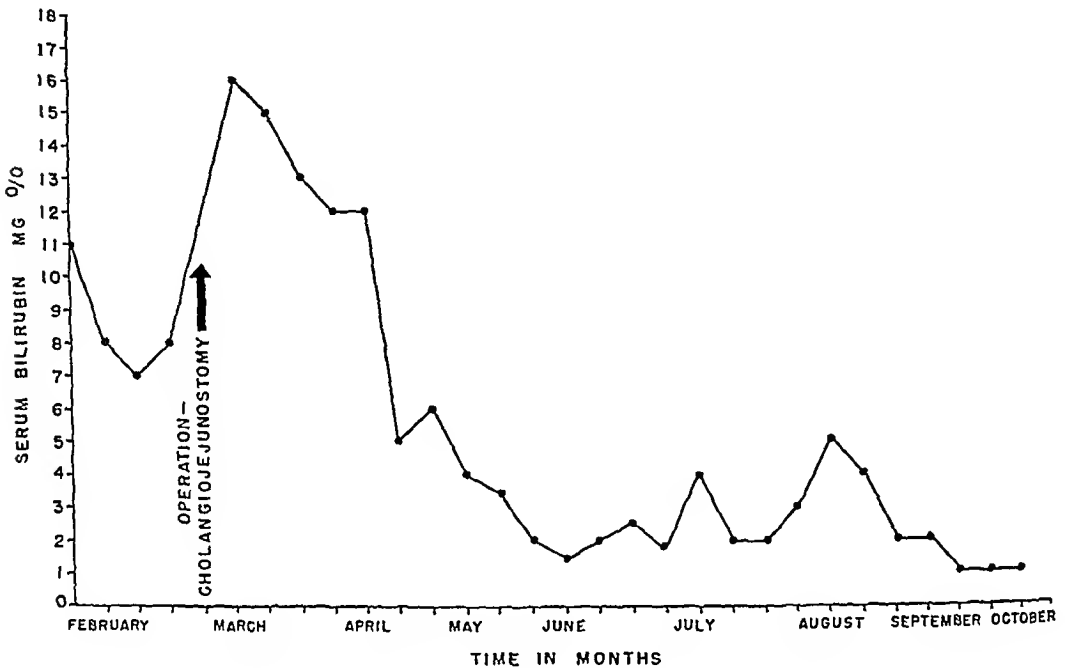


FIG 5—Serum bilirubin determinations before and after liver resection and intrahepatic cholangiojejunostomy

On March 13, 1948, this procedure was accomplished. A modified inverted V type of subcostal incision was used. The triangular ligament supporting the left lobe of the liver was divided and the left lobe of the liver delivered into the wound. The lobe of the liver was compressed between the left index finger and thumb while the partial resection of the liver was accomplished. Through-and-through overlapping mattress sutures were used to control bleeding from the cut surface of the liver.

A bile duct was found of size sufficient to allow the placement within it of a number 14 French catheter. Liver tissue immediately adjacent to the duct was curetted away in order to leave 5 mm of the duct protruding beyond the cut surface of the liver. A Roux Y loop of jejunum was utilized to make an end-to-end anastomosis between the jejunum and the bile duct. Care was taken to secure an accurate mucosa-to-mucosa anastomosis. The anastomosis was performed over a catheter and the catheter was brought out the jejunum in the Witzel manner.

Microscopic examination of the portion of liver removed showed the presence of a rather diffuse hepatitis. There was an increase in the connective tissue in many of the periportal areas and there was also a rather extensive inflammatory reaction present,

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characterized by the presence of infiltration with polymorphonuclear leukocytes and with round cell infiltration

The immediate postoperative course was a stormy one characterized by fever. A partial wound disruption required secondary closure on the twelfth postoperative day.

Bile was noted in the stool on the third postoperative day and has continued to be present. The patient's general condition has gradually improved and he has gained approximately 20 pounds in weight. The patient states that he feels better than he has since the onset of his original biliary symptoms. He has returned to full time work as a stationary engineer. The serum bilirubin determination has returned to normal.

SUMMARY AND CONCLUSIONS

1 The gravity of common bile duct injuries is emphasized and the commonly used methods of repair are briefly reviewed.

2 No one method of bile duct repair is applicable to all cases.

3 Cholangiojejunostomy with partial hepatectomy offers a method of re-establishing continuity of the biliary tract in some exceptionally difficult cases where restoration of continuity by other methods has heretofore been impossible.

4 One case treated by cholangiojejunostomy and partial hepatectomy is reported.

5 Regardless of the type of treatment used in re-establishing continuity, such patients are subject to the possibility of recurrent difficulty over a period of years.

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DISCUSSION—DR FRANK H. LAHEY, Boston. I am sure that it is of value to all who have to deal with stricture cases, to be aware of the various methods that can be used, because anyone who has dealt with many of them will willingly admit that they are difficult, that they are often unsatisfactory and that, no matter what is done, eventually many of them get into trouble again. On the other hand, I believe we should present the results of our experiences to bear out what the author has stated, that is, any method that does not preserve the sphincter is not as good as one that does. It will be impossible in some cases to do an end-to-end anastomosis, as Doctor Cattell and I have tried to bring to everyone's attention. We are not sure whether or not we devised this, and we do not care. We do know that it is not recognized and utilized as a method as often as it should be, and we have urged its use on every occasion when we have discussed this problem.

We want to stress these things again. If a bile duct is injured it is not the common duct in most cases, it is the hepatic, the high hepatic that is injured. This means that that portion of the duct in the pancreas, behind the duodenum, is protected from injury and is

therefore available if it can be found, and it can be found in almost all cases if you know how. I have been unable to find it once or twice, but on at least one occasion when I did not find it, autopsy revealed that it was there and I should have found it. It often takes hours, literally, it takes a tremendous amount of pains and patience, with the bleeding that comes from splitting the head of the pancreas. It takes mobilization of the duodenum. It is difficult, but it can be found, and it can be better found outside the duodenum in most cases than through the duodenum and trying to find the papilla. The papilla within the duodenum is difficult to find, the duodenum bleeds, the papilla is lost in the duodenal folds. You can often come upon it, but if you do not it is difficult to know at what level to make the incision in the duodenum at such a point that it is easy to find.

If you can find that portion of the duct which is in the head of the pancreas, and if you can split the edge of the pancreas, you will remember that the duct is well vascularized by its own blood supply, because it has annoyed you more than once in operating for common duct stones. If you can mobilize it you can mobilize the head of the pancreas, and you can mobilize the duodenum so that you can usually get it up to the end of the cut hepatic duct.

Regarding the operation of anastomosis of the left hepatic duct in the left lobe of the liver to the jejunum, the point I would like to make in connection with this operation—and I have no desire to condemn it or to detract from its originality—is that I believe when the left hepatic duct can be anastomosed to the jejunum by amputating the left lobe of the liver, a good section of common hepatic duct will of necessity remain, to which, with the mobilized common duct, a direct anastomosis can be made and thus preserve the sphincter. We have had Doctor Meissner, who is associated with Dr. Shields Warren in pathology, do a number of corrosion specimens for us, injecting the bile ducts with a plastic material. We believe that the two duct systems are largely separate and, as shown by these corrosion specimens, the left lobe of the liver has a bile system which comes down to the left hepatic duct to join with the right hepatic duct, the right lobe largely having a biliary tree and hepatic duct of its own. We believe there are almost no communicating branches that are of any great value, if there are communicating branches they are small and of relatively little value even, I believe, with dilatation. I would like to make sure that everyone understands this point—that this operation of implanting a left hepatic duct into a jejunum has no advantages over implanting a common hepatic duct into the jejunum, which can be done if common hepatic duct remains, and does have the disadvantage of not making use of the sphincter.

Doctor Cattell has developed a plan for patients who have only the two intrahepatic ducts left, which you will find valuable. I reported at the last meeting of the New England Surgical Society 227—not operations—but 227 patients with stricture of the bile duct upon whom we have operated. These strictures have been of all kinds and the patients have been through all kinds of procedures before coming to us, that series is now around 235. What often makes this operation of duct mobilization and direct anastomosis so difficult in cases in which we would like to employ it, is that the patients have been operated on so many times that the common hepatic duct is completely destroyed. I have just operated on a patient who had been operated on seven times, Doctor Cattell has just sent one home who had eight attempts at repair. In those cases there is no common hepatic duct left, they are all intrahepatic divisions, and in dealing with these stricture cases one must learn to dissect the intrahepatic duct out of the liver with the fulguration apparatus. You have to learn to demonstrate them within the liver as individual ducts. What Doctor Cattell has done that I think is a real contribution, is to approximate the intrahepatic duct divisions by intraductal suture, to convert two ducts into one, split them, and then put a Y-tube up one and a straight tube down the other for anastomosis to the end of the common duct. Many of these are not going to be great successes, but if the sphincter is preserved the patient has a better chance than if it is not preserved.

We know that the Lord will help you on many of these cases. He has to—and everyone knows our golf pro who has been around the clinic so long. We have performed

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seven operations on him, he has now gone three years since the last anastomosis, is well and has won several golf tournaments. He has had rubber tubes and vitalium tubes put in and now has a successful direct anastomosis. I plead with everyone not to go through what we went through originally—if it is avoidable, and sometimes it is not, that is, makeshift procedures, such as implanting tubes and anastomosis of hepatic ducts to bowel. We should try to do an operative procedure that offers a chance of getting the patient permanently well, and avoiding if possible ascending infection. All patients with duct anastomosis and tube implantations do not have ascending infection. Some of the jaundice attacks they have are the result of recurrence of stricture. I do not mean to say that end-to-end anastomosis will abolish those, they will occur just the same, but when a good mucosa-to-mucosa anastomosis is obtained it will produce a better result than any of these makeshift procedures.

This is so trite that I blush every time I say it, but we ought to concentrate on giving more attention to publicizing how dangerous cholecystectomy is. We realize that cholecystostomy has been almost abolished, but thousands of cholecystectomies are being done every day and each one is a possible stricture. If the patient died instead of recovering after injury to his ducts, in many cases he would be better off than to live with what he has to go through in the way of expense and suffering. We should publicize the fact that cholecystectomy is a dangerous operation. It is dangerous unless one realizes how important it is to control the blood supply, to demonstrate definitely the anatomic relationship, and to realize that anomalous anatomy is very common. I believe we could do nothing better than to write more and more on the need for accuracy in cholecystectomy, and recording the finding of the common duct in the pancreas and behind the duodenum.

I believe that many tend to say—"Oh, I cannot find that duct in all that scar tissue." You can. If you will lift the head of the pancreas where it projects to the right beyond the duodenum, if you will mobilize the edge of the duodenum by freeing the vascular external edge that bleeds so and annoys you, and roll it in, you can find it if you are patient. Then if you find the common duct in the head of the pancreas you can mobilize it, and you can put the ends of the common and hepatic ducts together in many of the cases. It is surprising how much duct is left when you have exposed it. You must remember that the duct does not go straight down, it goes over and then down, and when it is freed it becomes straight. In many cases these ducts can be put together up in the hilum of the liver. If a T-tube is inserted it must be left in a minimum of a year, it must not go through the anastomosis but in a slit below, with the upper limb up through the anastomosis. It must be irrigated daily or night and morning, or it will block, it will occasionally need ether injections. If left in for a year, in many instances the results will last and will be better than those obtained with other methods.

I would not have you think that we say this operation can be done on every case because we know that is not so, but I do want to say that with experience you will be surprised how often you can find a good length of the duct and how often you can put the two ends together which, after all, is the most physiologic of all operations for stricture of the bile ducts.

DR R. L. SANDERS, Memphis. It is a pleasure to discuss this paper, particularly since it was presented by one of our younger surgeons on his first appearance before this Association. Doctor Longmire, who originated the operation described, and Doctor Wilson have both recently become professors of surgery, Doctor Longmire at the University of California and Doctor Wilson at the University of Tennessee, and both are to be congratulated on the fine work they are doing.

Doctor Lahey has just expressed much of what I wanted to say. Every surgeon will agree that, if possible, defects of the ducts should be repaired by end-to-end anastomosis. Occasionally, one encounters a case, such as that reported by Doctor Wilson, wherein the duct has been destroyed so completely that nothing remains to bridge the wide gap between the liver and the pancreas.

We recently had a case similar to that of Doctor Wilson, which I reported just last week before the Western Surgical Association. The patient, a lady 32 years of age, had had a cholecystectomy elsewhere and at the operation both the common and the hepatic ducts had been excised. A short time later she had become jaundiced and a tube had been inserted for drainage. At her first visit to us, 8 months postoperatively, the tube was draining bile-stained fluid, but she was still jaundiced, was having chills and fever, her liver was enlarged, and she had lost 20 pounds in weight. On exploration we could find only a short end of the duct down beneath the head of the pancreas. The proximal end had sloughed away up into the liver hilus and completely strictured, producing a bile cyst. After evacuation of the cyst, an hepaticojejunostomy was performed according to the Allen method. The operation was successful for a time. Eight months later, however, the patient returned, presenting the same clinical picture as before. We operated again, this time disconnecting the jejunum at the hilus, removing a large number of stones from a pocket in the liver and, since no duct could be found, resuturing the end of the jejunum into the liver hilus. The mucosa was not inverted, in the hope that by this measure the anastomosis might be successful. As before, the suture was made around a tube which was brought out through the jejunum below. The patient progressed satisfactorily for six weeks. The chills, fever and jaundice then recurred and were accompanied by abdominal pain and the passage of blood through the bowel. The liver was enormously enlarged. Despite medical treatment, her condition grew worse and it became apparent that something drastic must be done. Having in mind Doctor Longmire's operation, and with the inspiration of Doctor Wilson's success in the case just reported, I decided to try a similar procedure.

On exploration, the left lobe of the liver filled the upper abdomen, displacing the right lobe to the other side, and was in such poor condition that removal of the entire lobe seemed advisable. Before its removal, through-and-through mattress sutures were inserted along the dividing line between the lobes to control hemorrhage and, after removal, continuous sutures were inserted along the cut edge. The left hepatic duct was isolated for a distance of two inches as the lobe was being removed. An attempt was now made to draw up the common duct for anastomosis to this segment, but was unsuccessful. The jejunum proximal to the Roux-Y anastomosis formerly made was therefore brought through the transverse mesocolon and the side united to the end of the hepatic duct, mucosa being sutured to mucosa. A lateral enteroenterostomy was then made below. Finally, as a precaution against slipping, the jejunum was tacked to the under surface of the liver for some distance on both sides of the anastomosis with the duct, and to the transverse mesocolon at its point of emergence. The previously made hepaticojejunostomy was not disturbed.

To the present time, now more than six months postoperatively, the patient has been getting along well and has gained 35 pounds in weight. Her icterus index is still elevated, but the liver is decreasing in size. It is probable that, sooner or later, the duct will restricture, even so, the operation will have been worth while.

As stated in the beginning, such procedures as these should be employed only after every effort has been made to unite the two ends of the damaged ducts. When the occasion does arise, however, they may offer the solution, at least for a time, to the patient's serious predicament.

DR WALTMAN WALTERS, Rochester, Minn. I think we should congratulate Doctor Wilson and also Doctor Sanders, for putting to clinical application an experimental problem which Doctor Longmire worked out so well in Doctor Blalock's laboratory. It seems to me this is the very best type of investigation, in which we all should be interested. I have had on another occasion an opportunity to congratulate Doctor Blalock on the clinical application of certain fundamental principles which he and his associates have studied in the experimental laboratory and have then carried into the field of clinical

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surgery I think the presentation of these two cases today by Doctor Wilson and Doctor Sanders is really an epoch-making occasion and I want to congratulate them both

These are two or three points one could well consider, particularly in Doctor Sanders' case, in understanding the excellent results Doctor Wilson has obtained. With left partial hepatectomy and hepaticoenterostomy it stands to reason that there must be some collateral circulation between the ducts in the left lobe and in the right lobe, for if there were not, after the passage of the sixth month Doctor Sanders' patient would have continued to be jaundiced. Regardless of what the corrosion specimens show, and these were thoroughly studied 22 years ago by McIndoe and Counseller, there is no doubt that there is a communication between the two lobes of the liver, through their main hepatic duct when these ducts unite within the liver, as they do in most cases. Moreover, the possibilities are that, when obstruction occurs in the extrahepatic bile ducts, there is a greater tendency for an intercommunication than there would be under normal circumstances. I believe that is one reason why, if one is successful, as these gentlemen have been, with this procedure, there is reason to believe there may be sufficient communication between the two sides of the liver so that it will work effectively. I do not believe either Doctor Wilson or Doctor Sanders need be too pessimistic about future results, after all, if one can relieve the patient of a very serious condition in which there is serious damage to the liver, even if it be necessary later to do a somewhat similar operation or a variable one, I think a great deal has been accomplished.

I want to congratulate both these gentlemen for making a very fine contribution to surgery, and I also want to congratulate some of the younger surgeons who are doing experimental work, Doctor Blalock and his associates, Doctor Longmire and others who have applied clinically the principles which these gentlemen have learned in training young American surgeons.

DR HARWELL WILSON, Memphis (closing) Doctor Longmire, with whom I have discussed this problem, feels very definitely that, as Doctor Walters intimated, there is a definite communication between the right and left lobes through the caudate and quadrate lobes. In addition to making this statement, I would like to thank Doctor Lahey, Doctor Sanders and Doctor Walters for their discussions.

COMBINED SUPRADUODENAL AND TRANSDUODENAL EXPLORATION OF THE COMMON BILE DUCT*

HOWARD MAHORNER, M D

NEW ORLEANS, LA

FROM THE SURGICAL SERVICES OF DR HOWARD MAHORNER BAPTIST HOSPITAL AND
TOURO INFIRMARY NEW ORLEANS LA

THE OBJECTIVES of this presentation are to discuss the advisability of opening the duodenum at the time the common bile duct is explored, to present as evidence a group of cases to show that combined supraduodenal and transduodenal exploration of the duct at the same time offers certain distinct advantages over and above those obtained by only supraduodenal exploration of the common duct, and to show advantages gained by extending the T-tube draining the common duct into the duodenum

A brief recapitulation of the important steps in the development of surgery for benign lesions affecting the common bile duct may be interesting. The operation of opening the common duct above the duodenum for the removal of stone was first performed by Kummell,¹¹ who described the procedure in 1890, and by Thornton¹⁷ who first successfully performed the operation in 1889 and reported it in 1891. The procedure of removal of stones by incising the duct in its retroduodenal portion has been credited to Haasler,⁹ who described it in 1898. McBurney¹⁴ performed a transduodenal operation first in 1892. McBurney opened the duodenum, severed the ampulla and removed the stone, but he did not open the common duct above the duodenum. In 1898, he reported six cases with five recoveries. Kocher first performed a transduodenal operation in 1894. He cut through the duodenal mucosa into the common duct but did not sever the sphincter. The common duct and duodenal walls were approximated with sutures.

It is difficult to find in the literature the basis for the frequently expressed extreme aversion to opening the duodenum to obviate obstructions of the common bile duct. Undoubtedly it may be attributed to fear surgeons have of duodenal fistula and of the danger of infection and peritonitis. Another factor in their attitude may be the feeling that duodenal reflux or regurgitation of duodenal contents into the biliary tract can set up cholangitis and fatal infection in a high percentage of cases.

However, it is time for a new evaluation of the dangers of opening the duodenum with present technical methods and under modern chemotherapeutic measures. When the duodenum is opened for the exploration it should be carefully mobilized, the superior leaf of the transverse mesocolon should be cut and pushed back. A longitudinal incision in the descending portion of the duodenum should be closed transversely, securely and carefully. I prefer running fine chromic catgut for an inner suture and interrupted silk for the outer

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 8, 1948

EXPLORATION OF THE COMMON BILE DUCT

If the duodenum has been mobilized, secure closure more readily may be effected

Duodenal reflux may not be so dangerous as it has been regarded. Whether it often causes symptoms may be debatable. I have left tubes in the common duct anastomosed to the jejunum after pancreatectomy for months before removing them and cholangitis did not result. Moreover, in those patients in whom we have pulled the end of the T-tube through the papilla into the duodenum after choledochotomy, no symptoms of cholangitis resulted.

The almost universally accepted method of releasing benign obstructions of the common duct is to open the common duct above the duodenum, and



FIG 1—Examples of extension of common duct drainage tubes into the duodenum as illustrated by postoperative cholangiograms. The transvaterian extension of the tube prevents the recurrence of stenosis at the duodenal opening of the common duct.

remove such stones as may be engaged with forceps or scoops, by aspiration and lavage of the ducts and by passing graded dilators (Bakès dilators) through the ampulla of Vater into the duodenum. Some surgeons question the advisability of forcefully dilating the lower end of the common duct and the ampulla with Bakès dilators.

Practically all surgeons in this country apparently feel that the best method of managing the common duct after it has been opened is to place a T-tube in it with short transverse limbs, so that "it can be easily removed" and so that the tube does not extend into the duodenum. Apparently one of the objections to passing the tube into the duodenum is the fear of permitting duodenal contents to regurgitate into the biliary system. To this attitude, and I believe to his credit, there is one man who has taken exception, and that is Richard Cattell, who has devised a long transverse limb common duct tube with the expressed intention of having one arm of the tube extend through the

common duct into the duodenum and even into the jejunum. Apparently the advantages to be gained by this have not been readily seen and accepted by surgeons in general. For there yet fails to be one authoritative article endorsing his tube and the idea, and many surgeons continue to show in postoperative cholangiograms short-arm T-tubes inserted in the common duct with definite or questionable filling defects.

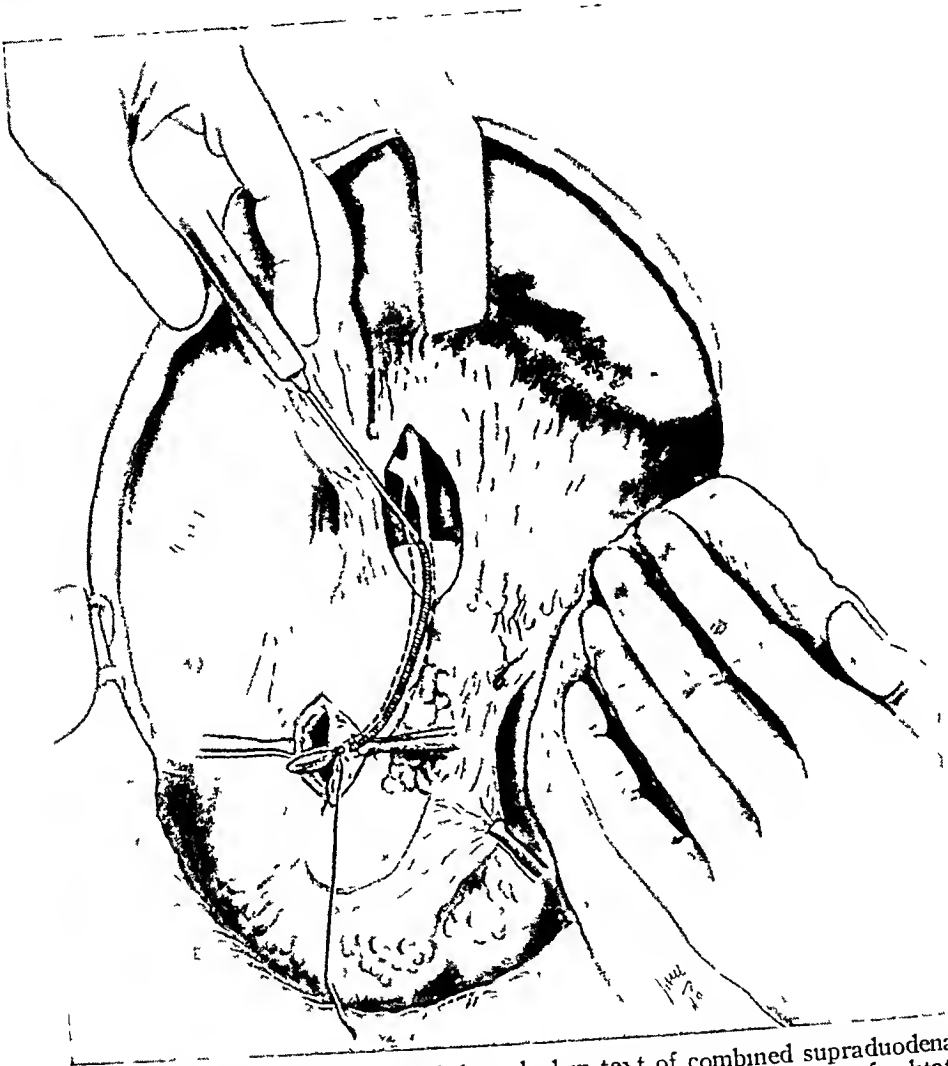


FIG 2—Illustrating method described in text of combined supraduodenal and transduodenal exploration of the common duct. In order to facilitate the introduction of the common duct T-tube and insure the passage of its lower arm into the duodenum a piece of silk is tied onto the Bakes dilator and is withdrawn through the common duct.

On my private services I have opened the duodenum and the supraduodenal portion of the common duct in 16 cases when exploring the common duct. This is admittedly a relatively small group of patients. Even in this small number information has been obtained which has really surprised us. No death resulted in this group of patients. Instead of using shortened transverse T-tube arms which would remain in the vicinity of the opening to drain the

EXPLORATION OF THE COMMON BILE DUCT

supraduodenal portion of the duct I have left one aim long and have deliberately pulled it into the duodenum, having the T-tube jut beyond the ampulla of Vater. Usually an ordinary T-tube is employed. Occasionally these are too short and a Cattell tube is used. This will prevent the recurrence of stenosis if the tube is left in for a sufficient length of time.

Stones were found in 11 cases and stenosis of the ampulla of Vater, or the lower end of the common duct, was found in four. A false impression was



FIG 3—After the Bakès dilator is withdrawn the silk threaded thus through the common duct is attached to the uncut horizontal limb of the common duct T-tube and the tube is drawn into the duodenum.

gained in three instances that the probe had traversed the papilla when it actually had not. In three patients a Bakès dilator introduced through the supraduodenal opening of the duct and felt through the duodenal wall as apparently in the duodenum, was ascertained, after opening the duodenum, to be still in the ampullary portion of the common duct and had not come

through the opening in the papilla which was definitely stenosed. When there is little or no inflammatory reaction or edema in the region of the common duct the pancreas is quite mobile, and with a small Baké's dilator it is possible by feeling through the unopened duodenal wall the point of the dilator, to gain the impression that it is actually in the duodenal lumen, when such is not the case. Such a false impression may be one factor in the recurrence or persistence of benign obstructions of the common duct.

TABLE I—*Operations Primarily for Benign Lesions of the Biliary System*

Cases	78
Cholecystectomy (without exploration common duct)	56
Cholecystectomy (and exploration duct 26%)	20
Exploration duct without cholecystectomy	2
(During gastrectomy 1)	
(Duodenal diverticulum 1)	
Duct explored duodenum opened	16
Duct explored duodenum not opened	6
Jaundice	14
Jaundice from stenosis (no stones)	3
Stones common duct	14
Stones common duct, no jaundice	3
Death (1) supraduodenal (only) exploration duct	

Stenosis (once with a duodenal diverticulum near the opening of the common duct) was found in four instances. By stenosis is meant a contracture at the opening of the duct into the duodenum which will not pass a 3-millimeter dilator without undue force or cutting the papilla. Perhaps stenosis may explain the high percentage of cases in reported series in which stones are known to be accidentally left in the common duct or reformed after supraduodenal exploration of the common duct had been performed. Certainly many

TABLE II—*Duodenum Opened (During Common Duct Exploration) 16 Cases*

Unexpected findings	
Stenosis at papilla of Vater	3
(Baké's dilator failed to pass into duodenum)	
Inflammatory mass region of ampulla	1
Passage of residual stones	1
Papilloma papilla of Vater	1
(Stones in common duct)	
Stone in head of pancreas	1
Duodenal reflux	3

of the cholangiograms which are shown in an effort to demonstrate absence of stones or presence of stones after operation show a very decided partial obstruction at the ampulla. Possibly this is ampullary contraction but it may also be stenosis which would be disclosed by the combined operation. In those instances where severe stenosis was found in our cases the ampulla was cut.

We found other surprising conditions when the duodenum was opened which had we not opened it might have been overlooked. In one instance a hard inflammatory lesion of the duodenal wall was found near the ampulla of Vater.

causing stenosis. In another instance a patient who had been explored at a renowned institution elsewhere twice within the last three years and stones removed, came to us with recurrent common duct obstruction. We also removed stones through a supraduodenal opening in the common duct, but on opening the duodenum we found a large papilloma, soft and easily overlooked unless the duodenum had been opened and affecting the ampulla of

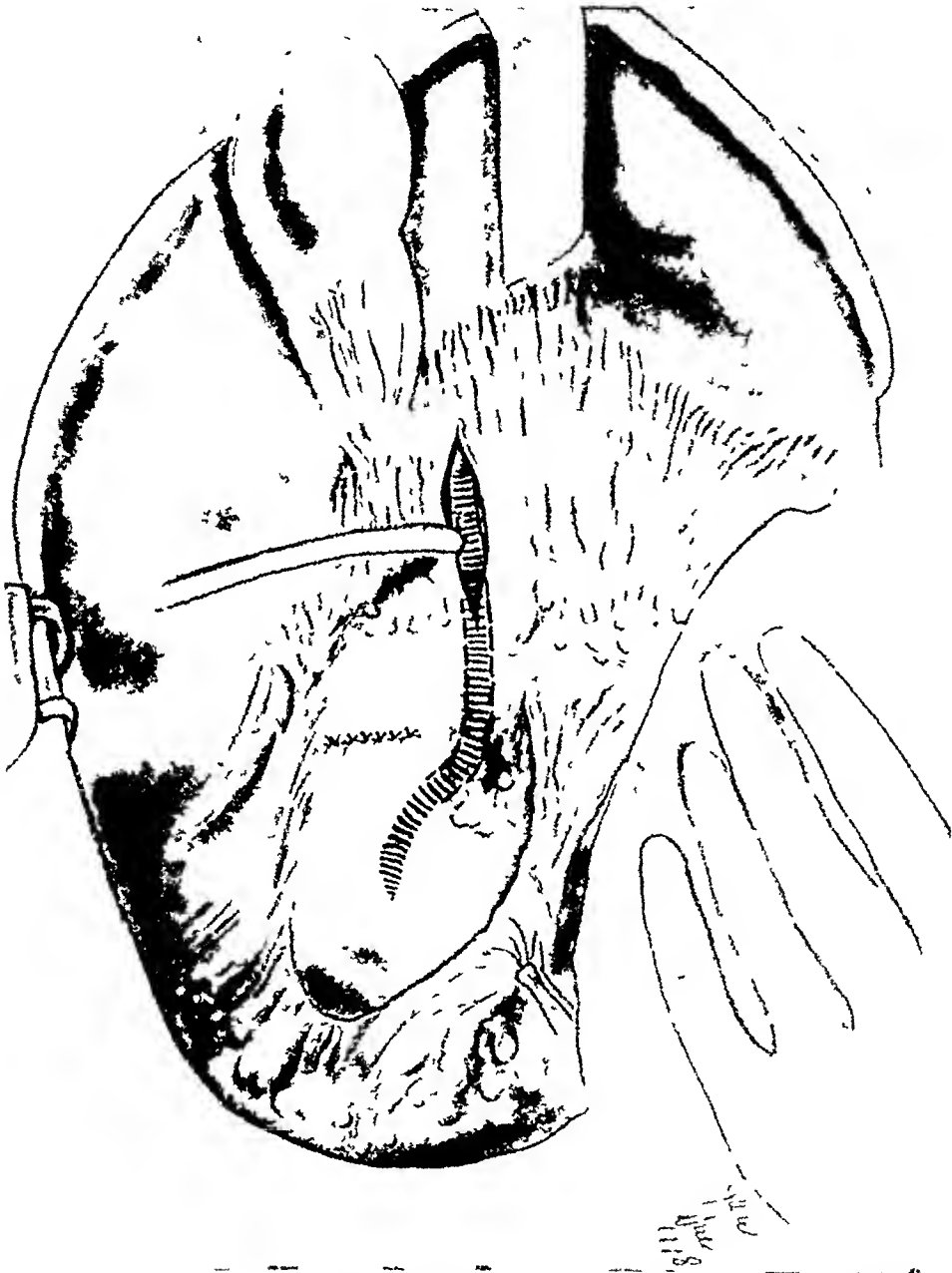


FIG 4—After the T-tube is placed in the common duct the supraduodenal opening is closed around the T-tube. The duodenal opening is closed transversely and with care to obtain security. The gallbladder is then removed.

Vater. This was removed, the common duct was transplanted into the superior surface of the duodenum and the upper end of the residual intrapancreatic portion of the common duct was closed off by inverting sutures. Because the patient's condition was such that he could not stand pancreatec-

tomy at the time, it has been deferred until he can gain a little more strength. This is a recent case. The patient recovered and has returned to his home in another city. He has gained weight and strength. Another operation will be done in the near future with intention of removing the remaining lower portion of the common bile duct.

In two instances the Bakê's dilator made false openings around the stone, once through the pancreas and once through the common duct into the duodenum above the ampulla of Vater. In each instance the stone was removed by transduodenal approach combined with the supraduodenal approach and the patient recovered. In one instance, we have reason to believe that we left

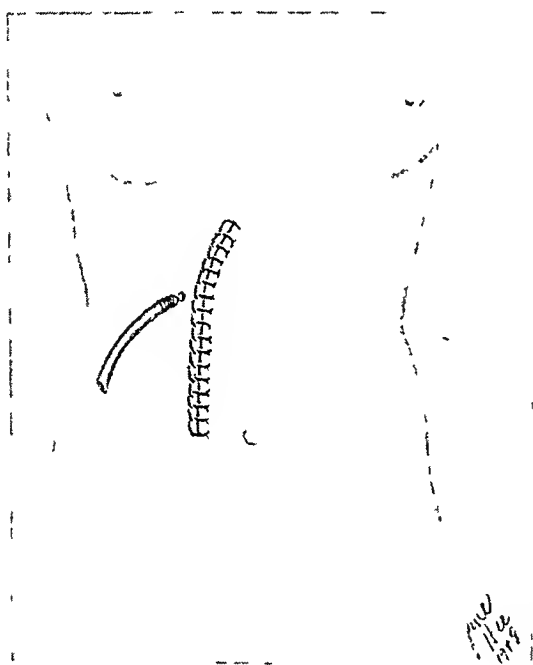


FIG 5—After exploration of the common duct super- and transduodenally and removal of the gallbladder the area is lavaged with saline and the common duct tube and a Penrose drain are brought through a separate small subcostal wound.

three calculi in the common duct. This patient had had a combined supra- and transduodenal exposure and an ampullectomy for numerous stones contained in the gallbladder and common duct. Postoperative roentgenograms showed shadows which we believed to be stones in the common duct. Subsequent studies showed the disappearance of these stones. We believe that they were passed into the duodenum due to the fact that the lower end of the common duct was widely opened.

We have encountered reflux of duodenal drainage, not only through the tube in a number of instances (in almost all cases this may be obtained by suction), but also around the tube in three instances in which it was very severe. All of these patients recovered. It is undoubtedly undesirable to have this as a complication, but it is also undoubtedly not nearly

so dangerous as it has seemed to be regarded by surgeons in general.

These 16 cases of supra- and transduodenal choledochotomy occurred in a group of 78 primary operations on the gallbladder and the bile ducts. By primary operation is meant operations directed to the biliary system itself and not to gastric or small intestine or other lesions. Moreover these cases only include nonmalignant lesions*. In this group cholecystectomy has been performed alone in 56 cases, cholecystectomy and exploration of the common duct in 20 cases. Thus the common duct was explored in 26 per cent of the

* Two exceptions, papilloma of the ampulla (because he had stones) and 1 gastric resection where the common duct was intubed by supraduodenal and transduodenal approach.

cases Exploration of the duct without cholecystectomy was done twice, once because the duct was intubed during a gastrectomy for ulcer which had penetrated onto the head of the pancreas and once for operation for duodenal diverticulum

There was one death in the entire series of 78 cases, and this occurred in a patient who had cholecystitis and cholelithiasis, choledocholithiasis and hepatitis We operated upon him under unfavorable conditions and when he had high fever, feeling that his condition was deteriorating and that we must hasten to give him a chance of survival The supraduodenal portion only of the common duct was opened, stones were removed and a T-tube was placed in the common duct The gallbladder was removed Another patient in which a cholecystectomy was done during the course of an operation which was performed for resection of jejunum for diverticula, died The judgment at operation was that cholecystectomy would add little to the risk and it was done The patient died of peritonitis This case is not included because it is not considered an operation primarily directed to benign lesions of the biliary system The major problem was of another character Another case is excluded in which a cholecystostomy was done but the operation was performed for filling defect, (polyposis) of the stomach in an 80-year-old woman In two instances, in addition to the above we removed the gallbladder for carcinoma, once in conjunction with resection of the transverse colon onto which the carcinoma had spread Both of these patients recovered

SUMMARY

A group of cases is reported in which the exploration of the common duct was carried out both supraduodenally and transduodenally There were no deaths from the 16 operations Simultaneous supra- and transduodenal exploration of the common duct revealed at times unexpected pathologic findings, such as stenosis of the ampulla of Vater, unexpected neoplastic and inflammatory lesions of the ampulla, residual stones in the lower end of the common duct The duodenum may be opened without an appreciable increase in risk to the patient and it probably insures the surgeon and patient against persistence of conditions which primarily led to the formation of stones in the common duct

Routine intubation of the common duct with a T-tube following exploration, always with the lower end of the tube traversing the opening in the papilla and entering the duodenum is advocated This will tend to keep the ampulla open and prevent recurrence of stenosis if it has been present It is an additional safety factor to permit the passage of small stones when the tube is removed because of the widely dilated papilla of Vater The dangers which have been attributed to duodenal reflux probably have been in the past greatly exaggerated

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DISCUSSION—DR WILLIAM F RIENHOFF, JR, Baltimore I have enjoyed Doctor Mahorner's presentation very much and heartily subscribe to his idea of transduodenal removal of gallstones which are impacted in the ampulla of Vater It has been our custom to make a small incision in the anterior wall of the duodenum parallel with its long axis and over the area in which the impacted stone is palpable The duodenum once opened, the impacted stone at the ampulla may be delivered up into the wound without difficulty, and incision made in the ampulla with subsequent delivery of the stone Also, any stones which remain in the common duct may be milked down with great ease It has often occurred to me that this might be the method to be preferred for removal of a stone of the common duct, rather than opening the duct above the duodenum

The technic I have employed in closure has been to suture the mucosa of the common duct about the duodenal mucosa through the entire thickness of the wall of the duodenum with interrupted "o" catgut sutures The incision in the anterior wall of the duodenum is then closed in the opposite direction as in a Hemeke-Mikulicz operation

With regard to drainage of the common duct with a rubber tube for the ordinary run-of-the-mill case of common duct stone, to be differentiated from those cases in which the common bile ducts are full of smudge or bile stone mud, it has been our custom for the past 20 years to avoid placing a tube of any type in the common duct In 1919, when the late William S Halsted was recovering from the first operation on his common duct for removal of a common duct stone (which operation was performed by R H Folles, Sr), a T-tube was inserted into the common duct At that time I was medical interne on the service of Dr Thomas R Boggs, who was Doctor Halsted's physician After removal of the T-tube drainage of bile persisted for a long period, and Doctor Halsted's

interest in drainage of the common duct was vigorously renewed. It is to be remembered that his first interest in drainage of the common duct began, I believe, when he performed the operation for the first time on his mother in Albany, New York, at which time he removed a common duct stone.

It was realized by Doctor Halsted and Doctor Finney, Sr., that the use of the T-tube in draining the common duct was not only an impractical method, but that when the tube, regardless of how the T was constructed, was removed, the suture line in the common duct was damaged to a greater or lesser degree. This was due to pulling out the tube, which was placed in the duct in those days, through the incision that had been made to remove the stone. The disparity of the opening in the duct and the size of the drainage tube was corrected by means of suturing the incision in the duct about the tube.

After joining the surgical service it was my opportunity to assist Doctor Finney, Sr., for a number of years, and it was he who first suggested closing the opening in the common duct and placing a drainage tube in the cystic duct if the latter were large enough, or, inserting a tube through a separate small opening cephalward, above the original suture line. As a rule, this secondary incision would be made at about the junction of the common hepatic duct and cystic duct to form the common duct. In this manner, a catheter inserted into the common hepatic duct through a separate incision, or one inserted into the cystic duct, could be removed without disturbance, by pulling the suture line in the common duct. This was first employed by Doctor Finney, Sr., and later, at the suggestion of Doctor Halsted, Dr. Mont Reid operated on a number of cases, draining the common duct via the cystic duct, or through a separate small opening in the common hepatic duct if the cystic duct was too small to receive a catheter.

Later, in 1923, when I began my residency in surgery, I discussed drainage of the common duct many times with Doctor Finney, Sr. It was decided to abandon drainage of the common duct in all cases of common duct stone, except those in which there was bile stone smudge or mud present. The technic employed was to open the common duct just above the duodenum, remove the stone or stones, and then insert a uterine sound through the common duct and the ampulla of Vater into the duodenum to be sure that the tract was clear. By this method the sphincter of Oddi was of course dilated in a manner similar to that following dilation of the external sphincter ani, and remained flaccid for some unknown period following dilation. No particular dilators were ever employed, the uterine sound being of standard size which traumatized the ampulla least of any instrument that could be passed through it to assure one of its patency. The opening in the common duct was then closed with interrupted fine silk sutures. The abdomen was always drained with two protective cigarette drains.

For a period of 20 years, with few exceptions, the common duct has been closed in this manner. There is always some drainage of bile-stained serum for four to six days after operation, just as one would expect after simple removal of the gallbladder. There has not been a single instance of any complication resulting from closing the duct without placing a tube within it, and the convalescence of the patient has been much more comfortable, more physiologic and more rapid than if the bile were drained to the exterior through a tube. The dilated ampulla, even though this dilation is slight, allows the bile to proceed along its natural channel into the small intestine, and elderly patients particularly have a much less serious postoperative course. I am opposed to placing a tube in the common duct except under the conditions mentioned above, and I can see no necessity whatsoever for this drainage except in the presence of bile-stained smudge and never, in my opinion, should a tube be used in the ordinary type of common duct stone or stones encountered.

The argument is often used that if a stone is overlooked for some reason and left in the common duct it is better to have a T-tube within it, but this fails to be impressive because, as everyone knows, the stone cannot be removed through the T-tube and the patient will require re-operation in any event. Tubes carry infection, as all drainage tubes do, thereby subjecting the patient not only to the hazard of the infected wound, but

to the more serious problem of infected ducts with a greater or lesser degree of hepatitis

In the cases of reconstruction of the common duct which I have performed, in which it was possible to do either an anastomosis between the stump of the common hepatic duct and the duodenum or jejunum, or an end-to-end anastomosis between the common duct and the common hepatic duct, I have always placed an indwelling catheter running down into the duodenum. In some cases, depending on the length of the catheter in the duodenum, the tubes have been passed by rectum from two months to three years afterward, and in all cases the lumen of the tube has been completely filled with debris and bile salts which have been precipitated in the tube. The tube has served only as a scaffold and in no sense of the word as an actual canal.

It seems to me that, after these many years and the profusion of papers that have been written on drainage of the common duct, it is time the lack of necessity of placing a tube in the common duct should be brought before this Association.

APPLICATION OF TECHNIQS OF RECONSTRUCTIVE SURGERY TO CERTAIN PROBLEMS IN GENERAL SURGERY*

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IT IS OUR FIRM CONVICTION that reconstructive and general surgery should not be entirely divorced from each other as specialties. The plastic man loses much of the thrill of speculative diagnosis and the satisfaction which follows successful operations in matters of "life and death." If he has had no training in the basic sciences and in the fundamental principles of general surgery, moreover, the scope of his practice is extremely limited. He is apt to become a mere technician with his work confined within the rather narrow bounds of what is popularly known as cosmetic surgery. The general surgeon, on the other hand, misses the stimulation associated with the devising of reconstructive procedures to meet the needs of each individual case as it presents itself. He is deprived, as well, of the pleasure of being able to achieve results which are readily visible and which are of such great emotional and economic importance to the patient.

There are certain plastic principles which are equally useful in all types of "surface" operations and which should be included in the training of every young surgeon no matter what his specialty. First among these may be mentioned the correct placing of incisions to produce inconspicuous scars and to avoid postoperative contractures. In this connection it might be well to serve warning that many textbooks of surgery in discussing this problem use illustrations of Langer's lines of skin tension with vertical markings on the forehead, neck, cubital and popliteal spaces. The proper direction of skin incisions, however, is perpendicular to the action of the underlying muscles in areas where they are attached to the skin, as in the face. Where there is no attachment to the skin, incisions should be placed perpendicular to the direction of excursion of the skin which is produced by normal muscle pull. The most reliable guides are the normal creases of the skin whenever they can be employed. On the face, the shadow lines near the hair margins and the outline of the jaw often prove useful. In the cheek region or other area where it is impossible to follow a normal skin fold, incisions should be staggered to break up the scar line, which would otherwise catch the light and seem more prominent. The practice of making perpendicular incisions in the axilla and across joint creases, where the development of contractures is inevitable, is most deplorable but unfortunately all too common.

In the treatment of traumatic wounds, emphasis should be placed upon the importance of covering all raw areas at the time when the patient is first seen.

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 8, 1948.

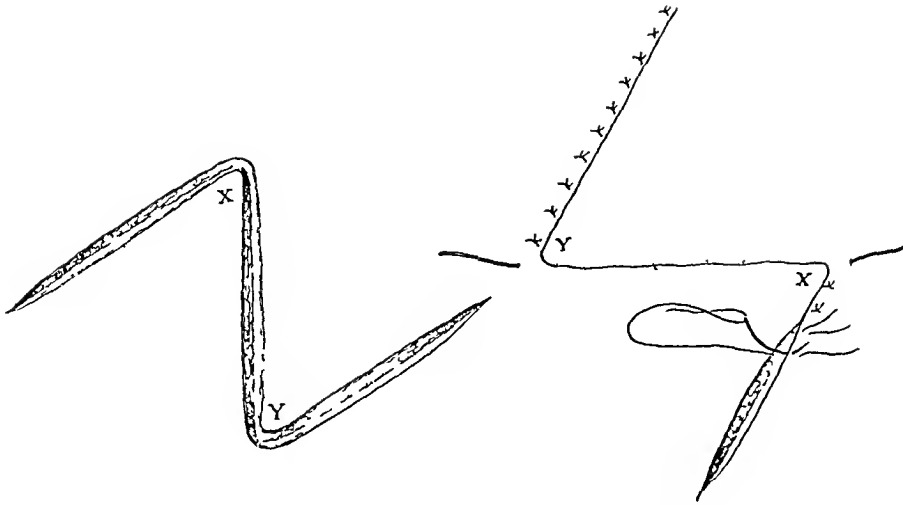


FIG 1—Diagram of the conventional Z plastic

unless lacerations are so contaminated that primary closure is too great a hazard. If the tissues cannot be closed otherwise, a temporary thick-split skin graft may be applied, in the case of an avulsion wound of the hand, a direct

flap may be constructed by burying the injured part into the opposite arm or the abdominal wall. The same principle of covering denuded areas as quickly as feasible applies to acute burns, where every effort should be made to prepare patients for at least preliminary grafting by the end of the third week with the use of pressure dressings, adequate chemotherapy and maintenance of normal blood volume and protein balance by repeated transfusions of whole blood.

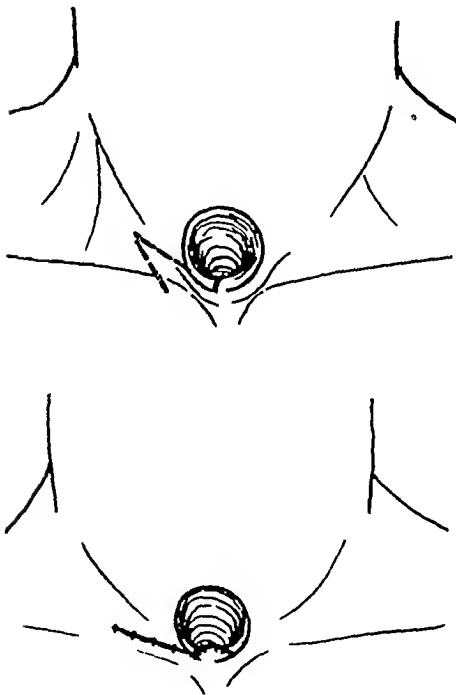


FIG 2—Diagram showing the application of a triangular flap in a permanent tracheotomy opening

It is often a temptation on the part of the surgical house staff, especially when confronted with a number of severe lacerations in accident cases at night, to sew up wounds as rapidly as possible with whatever suture material is at hand. Unfortunately, it is sometimes impossible to remove entirely at a later date a disfiguring scar or the marks of widely placed sutures which might have been avoided with a little patience and care. All wounds should be closed accurately in layers. On the face

and exposed surfaces, delicate suture material should be employed, stainless-steel wire gives rise to a minimum of local tissue reaction, and the results obtained with its use are well worth the additional time and effort required.

A pressure dressing should be applied in every case, as a matter of routine, to prevent postoperative edema and hematoma formation

Sufficient stress should be placed upon the necessity of undermining the surrounding skin to relieve tension on wound edges. If undermining alone is

not sufficient, the tissues may be re-arranged by the transposition of flaps of skin. The so-called Z-plastic operation, which has been popularized in this country particularly by John Staige Davis, Kitlowski and Ferris Smith, is one of the most useful procedures which the general surgeon may appropriate from the armamentarium of the plastic surgeon.

Figure 1 shows the general plan of the Z. Its underlying principle is the achievement of relaxation of the tissues along the central line as a result of the transposition of tissues from the margins of the area into the region of contracture or tension. The central limb serves as a common side of two triangular flaps. The two arms of the Z or reversed Z, as the case may be, are outlined usually at an angle of 60 degrees and blunted to avoid compromise of the circulation at the tips.

The contribution of technics of reconstructive surgery to general surgery we feel should not be limited, however, to those which we have just outlined,

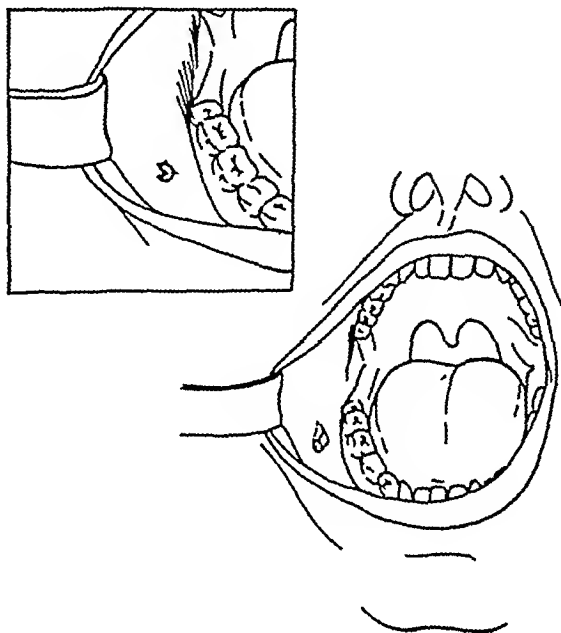


FIG 3—Diagram showing the use of a triangular flap in the repair of a parotid-duct fistula

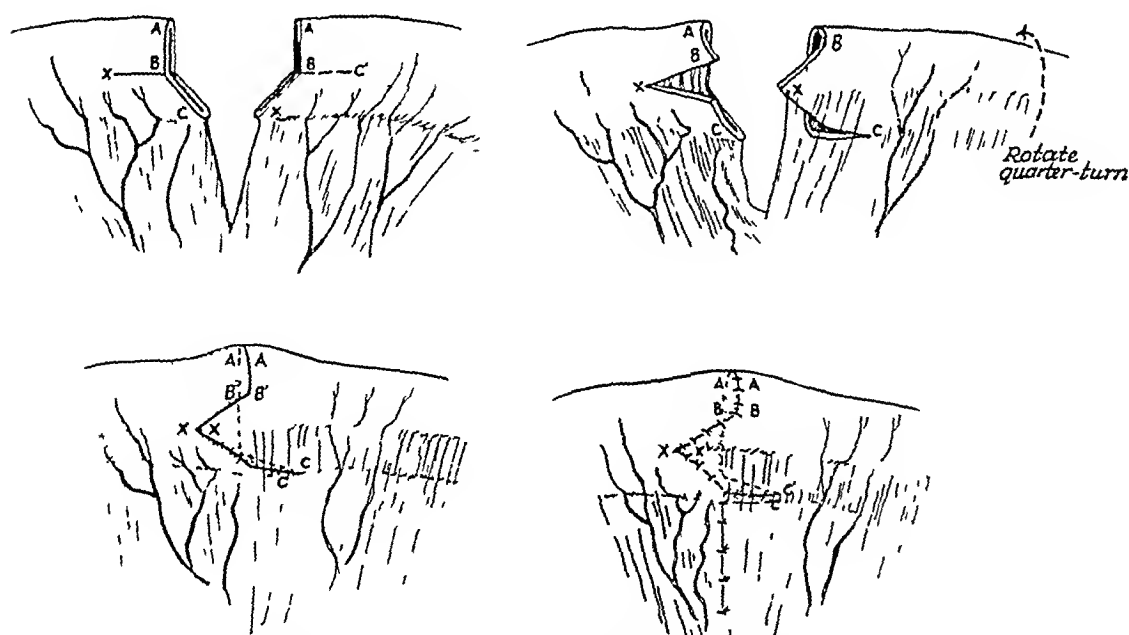


FIG 4—Diagram showing incisions for modified Z-plastic in an experimental hollow-tube anastomosed to prevent stricture

and we have recently decided to investigate the practicability of applying plastic procedures to problems in visceral surgery. Clinical and experimental work in progress deals with methods of preventing postoperative constriction.

The amount of stricture which develops from a circular scar depends upon the size of the lumen of the tube as well as on the quantity of scar-tissue formation. In the large and small bowel, therefore, obstruction following ordinary surgical procedures is something of a rarity. In tubular anastomosis end-on in other parts of the body, however, strictures are frequent and troublesome, especially where a viscus is anastomosed to the skin, as in a short, single-barrel colostomy, a tracheotomy, after laryngeal resection, and in certain stages of operation for repair of hypospadias when the normal urethra is sutured to the

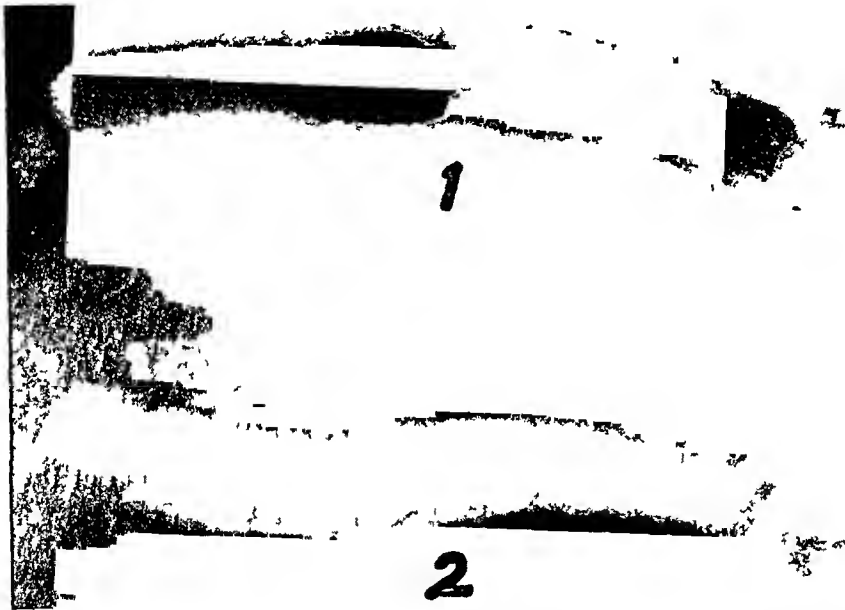


FIG 5—Roentgenogram five months after anastomosis in an experimental animal (1) Conventional type (2) Modified Z plastic

artificial skin-formed tube. For the prevention of scar contracture in these instances, we advocate the use of a small triangular flap of skin to be sutured into a V-shaped opening in the margin of the hollow tube. So far we have had very good results in several patients with permanent tracheotomies (Fig 2). This same method we employ in the repair of an external fistula of the parotid duct, which is dissected away from the cheek and brought into the mouth through a triangular incision.

The apex of the flap is sutured into a slit made on the side of the tube (Fig 3). This procedure has also been reported by Thomas Stevenson. In the reconstruction of the esophagus by a skin-lined tube, the anastomosis to the stomach is accomplished with an inverted V-shaped incision to place a triangle of normal tissue across the line of tension and thus avoid a circular scar. At the present time, work is in progress, in collaboration with Dr R M Moore and Dr A O Singleton, Jr, to study postoperative results in experi-

mental animals following the use of similar triangular flaps in the common bile duct

In addition to this preliminary investigation, we have been very much interested in devising a modified Z-plastic procedure to be employed in various types of tubular anastomosis to prevent stricture formation. In working out the method we have selected the small bowel of the dog as the most available material to observe for experimental purposes. In each animal a conventional end-on anastomosis was performed as a control, with the incision slightly oblique according to the usual practice. We next made in each animal a second resection and closure, employing a modified Z-plastic. In order to maintain abundant circulation, the triangular flaps which form the Z were placed in the mesenteric border of the gut. Incisions for resection were made as shown in

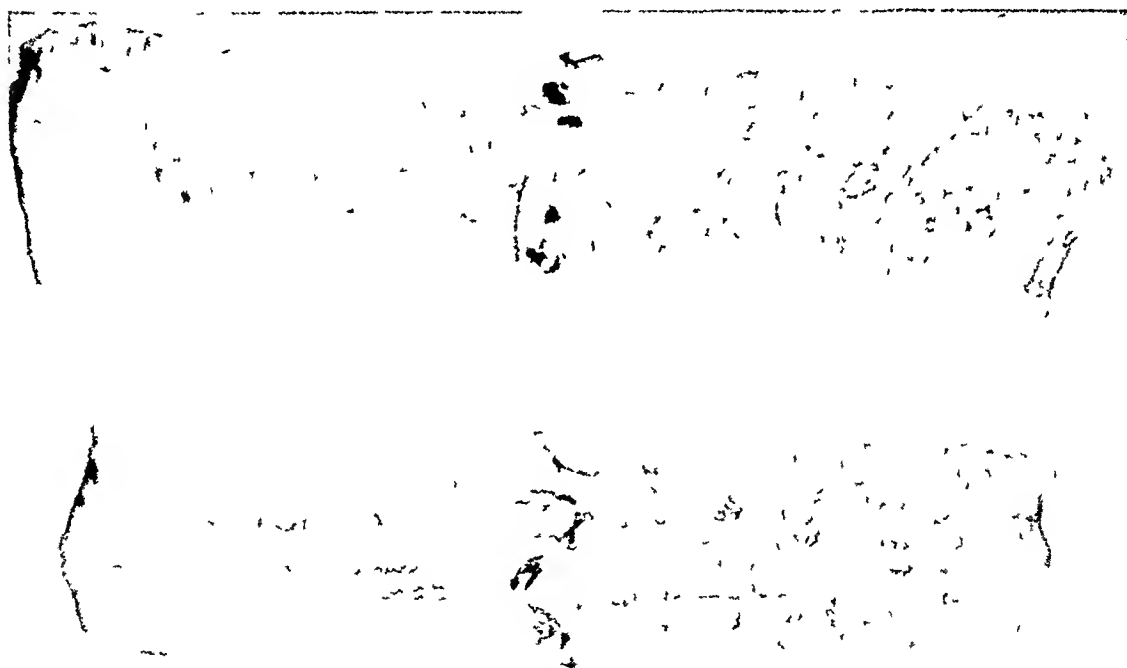


FIG 6—View five months after anastomosis in an experimental animal with the gut opened opposite the mesenteric border

the diagram (Fig 4). Perpendicular incisions were carried first midway through both sides of the bowel in each segment (AB and A'B'). They were then carried through the remainder of the bowel at an angle of 120 degrees down to the mesenteric border (BC and B'X'). A V-shaped portion of the mesentery was removed along with the resected bowel. Next a horizontal slit (BX) was made equal in length to the flap on the mesenteric border. A similar incision (B'C') was made on the other surface of the opposite side. Now with a quarter-rotation of the bowel the two flaps thus made were transposed, bringing together points X and X' and also C and C'. As may be noted, the mesentery now was present under each flap and the lumen of the bowel was considerably enlarged, as one would expect from the interposition of extra tissue. The procedures were carried out in eight animals, and after the lapse of

from three to five months there was still apparent, both by roentgen study (Fig 5) and direct visualization (Fig 6), an increase in the size of the lumen of the bowel in comparison with the site of the conventional anastomosis. We are hoping in the near future to employ the modified Z-plastic in smaller tubes where stricture often presents a genuine clinical problem.

CONCLUSION

Certain technics in surface operations which are considered to be within the province of reconstructive surgery are actually applicable to all branches of surgery and should be included in a comprehensive training program. The use of plastic principles in the solution of long-standing problems in general surgery is presented as a challenge which merits extensive laboratory and clinical experimentation.

DISCUSSION—DR E A KITLOWSKI, Baltimore. Unquestionably the use of Z-skin flaps in skin, rather than a linear incision, will offer better exposure and closure and will prevent many scar contractures which we have to contend with. In conjunction with the dressing Doctor Blocker mentioned in his excellent presentation, of necessity one must be a little careful that too much pressure is not exerted, for fear of interfering with the circulation of these flaps. Incidentally, in creating the flaps it is very important that the angles of the flaps be not made too sharp, so there will be no necrosis at the ends of the flaps themselves. I think if this method were applied as Doctor Blocker suggested to work inside the body, it would be a very important factor in the success or failure of the operation.

DR ROBERT E MORAN, Washington. I enjoyed this presentation very much. I am sure Doctor Blocker does not mean to infringe on the field of the general surgeon. I think he feels that there should be better co-operation between the plastic and the general surgeon. For example, in credentials for our Plastic Board, the plastic surgeon has to have one or two years of general surgical training. A general surgeon passing the Board seldom has the opportunity of any detailed training in plastic surgery. One important phase of plastic work is traumatic surgery as it comes into the general hospital. This is usually handled by the general surgeon, I speak now of automobile injuries in which there is a tremendous amount of damage to the face, etc. When one sees the case five or six days after the repair, the resident will say there was just too much bleeding to get good tissue closure, etc.

If you explain to the resident that the thing to do is to spread the wound wide and tie off the vessels, usually structures will be seen that we know go together. For example, in the old days we used to shave the eyebrows, but in severe injuries the eyebrow is an important landmark, the edge of the lid, the ala of the nose and the mucocutaneous junction of the lip are important. If we put together only tissues that we know belong together, we finish with a fairly good-looking face and there is little work for the plastic surgeon to do later. I have found that by talking to these residents and learning their problems, and having them come over on the plastic service for a few weeks, it has repaid splendidly by the fact that we seldom have to do much later with severe facial injuries.

DR R M MOORE, Galveston. Doctor Blocker has described a method for the anastomosis of small tubes which seems to have several applications in surgery. I am not sure of its usefulness in dealing with the intestine. Probably there is no particular need for it in anastomosis of the adult intestine, which is of sufficient diameter that constriction

at the site of anastomosis is not a great problem. A method is needed to facilitate anastomosis of very small calibre intestine such as that distal to an atresia in infants. However, in this situation, the disparity in the size of the proximal and distal loops would make Doctor Blocker's technic scarcely applicable.

In end-to-end repair of divided or strictured common duct, on the contrary, the technic appears very useful. Dr. A. O. Singleton, Jr., and I have been doing some experimental work upon the common duct in dogs and have taken occasion to test this method of anastomosis. In dogs of average size the common duct is almost too small for accurate anastomosis unless it has been experimentally dilated by ligation of the distal duct a week or two previously. If such a dilated duct is sectioned and the cut ends are then anastomosed by this technic, the zone of anastomosis appears a widening in the duct rather than a narrowing, and still has this appearance some weeks later. This suggests that the method would be advantageous in repairing other small tubes such as the parotid duct and the ureter. It may also be useful in arterial anastomosis.

The method Doctor Blocker has shown for preventing contracture at a tracheotomy stoma can be applied to prevent skin contracture about a colostomy opening.

DR. T. G. BLOCKER, JR., Galveston. I certainly thank the discussers of the paper. I want to repeat again that I am not trying to demonstrate a method of anastomosing intestines. My primary objective is to show the value of this technic and its possibilities in anastomosing tubes that have their circulation in their entire wall.

THROMBOSIS AND EMBOLISM*

THE FIVE-YEAR EXPERIENCE OF A SMALL GENERAL HOSPITAL

ROY C WIGGINTON, M D (By Invitation), WILLARD H PARSONS, M D ,
AND W KENDRICK PURKS, M D (by Invitation)

FROM THE VICKSBURG HOSPITAL AND CLINIC VICKSBURG MISSISSIPPI

DURING THE FIVE-YEAR PERIOD ending January 1, 1948, phlebothrombosis, thrombophlebitis or embolism occurred after 40 of the 9,230 surgical procedures performed at the Vicksburg Hospital. The incidence of these postoperative vascular complications in this series of consecutive, unselected cases thus was 0.43 per cent. Twenty-one patients developed thrombophlebitis and eight developed phlebothrombosis, the initial lesion being followed by embolism in three cases in each of these groups. Eleven other patients developed embolism after operation in the absence of previously recognized phlebothrombosis or thrombophlebitis.

This is a relatively small series of cases, it is true, but it seems worth presenting for several reasons. It illustrates the universality of this particular problem. It emphasizes again the type of operation and the type of patients in which and in whom this type of postoperative complication is most likely to occur. It demonstrates the possibilities of prophylaxis and of therapy by a hospital staff which has become increasingly aware of the risks of postoperative vascular complications. Finally, and most important of all, it carries the lesson of errors which should not have been made and the losses which should not have occurred.

INCIDENCE

This series bears out, first of all, the paradoxical situation which is generally prevalent in respect to thrombosis and embolism. Over the period—perhaps 10 to 15 years—in which these postoperative complications have been recognized as susceptible to prevention and amenable to treatment, their incidence has increased notably.^{1,5} In our own series there were five such complications in 1943 and the same number in 1944 against 16 in 1947, an increase out of proportion to the increase in surgical population of the hospital. The explanation, of course, for this as for a similar increase in most reported series, is that our recognition of these conditions has increased in proportion to our awareness of their possible development.

On the basis of the incidence reported in the literature, Barnes,⁵ after making due allowance for the selectivity of reported cases, estimated that each year 34,000 persons in the United States die of pulmonary embolism. Whether or not one accepts these figures without reservation, there is no doubt of the potential seriousness of postoperative thrombosis and embolism. The incidence of these complications was low at the Vicksburg Hospital, as it usually is in a warm or semitropical climate. But there were seven deaths in the 40 cases,

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 8, 1948.

THROMBOSIS AND EMBOLISM

which is a high case fatality rate. Furthermore, these seven deaths were concentrated in the 17 cases of embolism, which makes the case fatality rate in that group appallingly high and makes clear once again that the best method of reducing the mortality of postoperative vascular complications is to endeavor to prevent the conditions from which emboli arise.

ETIOLOGIC FACTORS

Naturally the situation cannot be reduced to such simple terms. Not a great deal can be done about many of the predisposing and contributing factors beyond the exercise of special precautions in the cases in which these factors are known to exist. Our prophylaxis at the Vicksburg Hospital includes the use, after all operations, of exercises for the legs, deep breathing,

Distribution of Lesions and Fatalities in 40 Postoperative Vascular Complications

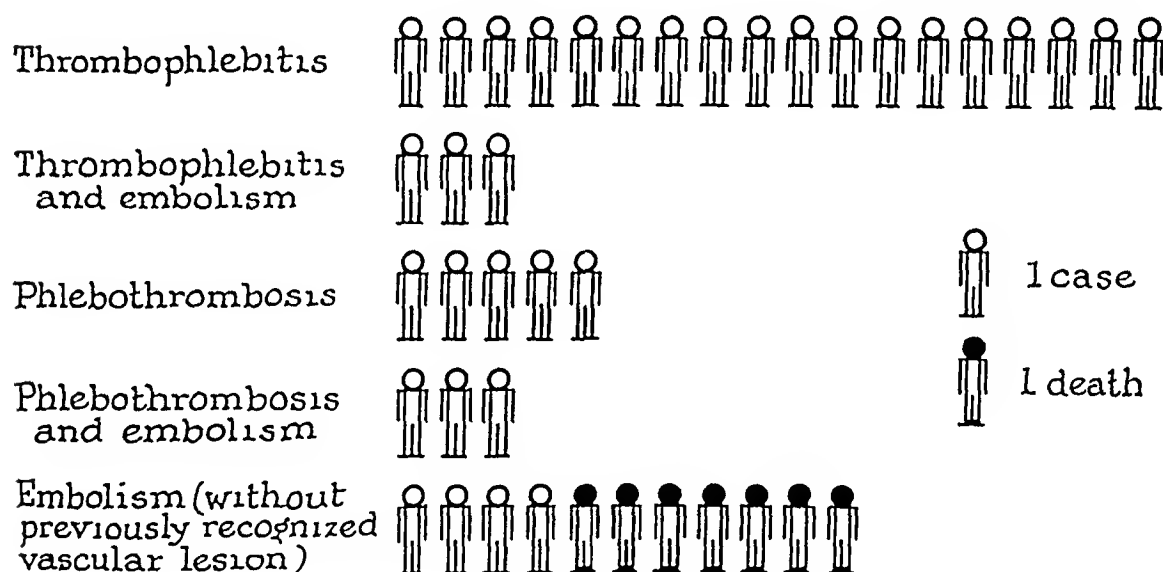


FIG 1

frequent changes of position, sedulous avoidance of Fowler's position and early ambulation. In special cases the lower extremities are wrapped in elastic bandages from the toes to the groin. Digitalis is given to patients with cardiac disease, especially those with a history of cardiac failure. These precautions, however, do not prevent the bewildering fatal cases of pulmonary embolism, which exist in all series. The catastrophe comes to pass without any hint in the patient's previous history or clinical course that it is impending.

The data in this series are in general accord with those in other reported series. The majority of the patients (32) were women. Ten of the 40 patients were Negroes, who seem about as prone as white subjects to develop vascular complications after operation. It may or may not be significant that four of the seven fatalities occurred in this race, but there is no doubt that four deaths in 10 cases is an extremely high case fatality rate.

The statement that the age range in these 40 thrombo-embolic complications

was 21 to 77 is of no particular significance until the figures are broken down. Then certain facts become evident:

1 Of the 22 patients in this series under 40 years of age, four developed embolisms, one of which was fatal.

2 Of the 18 patients over 40 years of age, 13 developed embolisms, six of which were fatal.

3 Every one of the seven patients in the series who was 60 years of age or over developed an embolism, either abruptly or following clinically evident phlebothrombosis or thrombophlebitis, and five of the seven lost their lives as a result.

A series of 40 cases is far too small to permit statistically significant conclusions, but these figures cannot be discounted because they follow so closely the experience of others in respect to the age incidence and mortality of pulmonary embolism.

Our experience is also in line with the general experience that vascular complications are more likely to occur after certain types of operations and after certain conditions than after others. In this series, 13 of the 40 vascular complications occurred after hysterectomy and represented 38 per cent of all the hysterectomies performed during the five-year period surveyed. Ten occurred after other intra-abdominal pelvic operations and five occurred after plastic procedures on the perineum. In other words, 70 per cent (28) of the 40 cases of thrombosis and embolism in this series occurred after pelvic operations. Even more striking is the fact that three of the seven fatalities in the series occurred after hysterectomy, two of which were for carcinoma, while three other fatalities followed operations for carcinoma of the stomach and carcinoma of the breast. These figures again may be too small to be of statistical significance, but that does not detract from their clinical importance.

Six vascular complications occurred after 220 operations upon the biliary tract or resections of the stomach or large bowel, an incidence of 2.74 per cent. Although vascular complications are uncommon following surgery of the upper portion of the body, this series includes one instance of thrombophlebitis following thyroidectomy and one fatal embolism following radical mastectomy. One case followed incision, drainage and application of a cast for osteomyelitis of the femur and two occurred after open reduction of fractures of the lower extremity, in all three cases, one of which was fatal, immobilization was perhaps the principal etiologic factor. In only one other case in the series, to be mentioned shortly, was prolonged bed rest an apparent factor in the development of the vascular complication. The remaining cases in the series occurred after inguinal hernioplasty, closure of perforated peptic ulcers and application of a pedicle graft to a varicose ulcer. There were no postoperative vascular complications in the few splenectomies performed for hemolytic disease at the Vicksburg Hospital over the five-year period in question, which is interesting in view of Priestley and Barker's⁶ contention that this operation is associated with etiologic factors likely to produce the highest recorded incidence of postoperative thrombosis and embolism.

Such predisposing causes as obesity, cardiac disease, blood dyscrasias, infection and extensive tissue resection which are commonly accepted predisposing factors in the development of postoperative vascular complications, were all present singly or in combination, in most of the cases in this series.

As has already been pointed out, in 11 of the 17 cases of pulmonary embolism in this series there was no evidence of a preceding thrombosis or thrombophlebitis which suggests that in all 11 cases the emboli arose on a basis of silent deep-seated phlebothrombosis. The fact that in no instance was a fatal embolism preceded by a clinically evident nonfatal episode can, we think, be accepted at its face value. The resident and visiting staffs in this institution are alert to the dangers of pulmonary embolism and no time is lost in the prompt institution of anticoagulant or other therapy as soon as the presence of a postoperative vascular complication is recognized or suspected.

This series differs from certain reported series in that clinically evident thrombophlebitis was considerably more frequent (21 cases) than clinically evident phlebothrombosis (eight cases). We do not wish to emphasize this

Age Incidence in 40 Postoperative Vascular Lesions

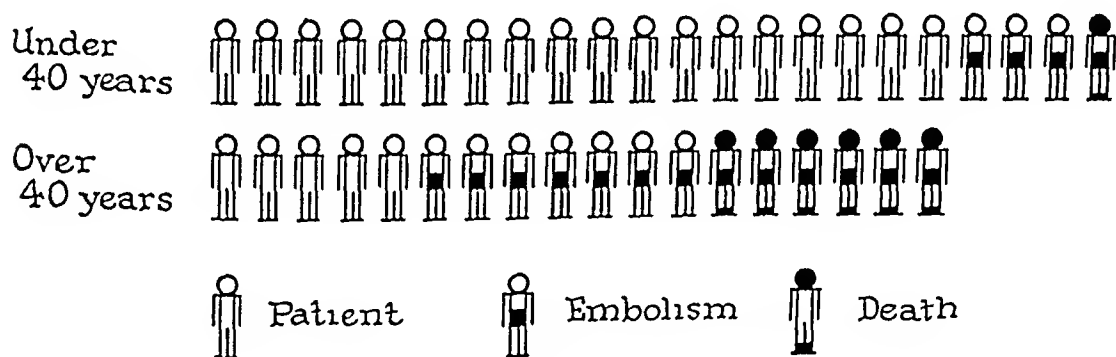


FIG. 2

disparity unduly, since it is apparent rather than real. In the remaining 11 cases, all of embolism, as has just been pointed out, phlebothrombosis was presumably present but was not clinically evident. On the other hand, it would be well to emphasize that pulmonary embolism may occur after the inflammatory vascular complication quite as well as after the so-called bland variety. Furthermore, as collected series prove, thrombophlebitis followed by embolism is fatal in perhaps 5 per cent of all cases.⁷ It, therefore, seems wise to view it with considerably more concern than some authors now suggest it merits.

DIAGNOSIS

The postoperative vascular complications which make up this series were diagnosed chiefly on the clinical evidence, which was unmistakable in all cases. Roentgenograms of the chest were positive in only two of the five cases in which they were made, and electrocardiograms were positive in only two of four cases. The preponderance of negative findings is not surprising because,

with a single exception in each group, these examinations were made in non-fatal cases, none of which was very severe. The majority of patients with fatal embolism died too promptly—four of them within 10 to 35 minutes of the onset of symptoms—to permit diagnostic studies, even if they had been necessary.

Phlebography, as a method of diagnosing phlebothrombosis antecedent to embolism, was not employed in any case in this series. It has not been widely used, and one receives from the literature the impression that it is even less popular for this purpose at this time than it was when first introduced. How misleading this method of diagnosis can be is evident in the case mentioned by Linton,⁸ in which a patient with normal bilateral phlebograms died 48 hours later from massive pulmonary embolism.

THErapy

Since June 1, 1944 it has been the general policy at the Vicksburg Clinic to treat phlebothrombosis and thrombophlebitis with dicoumarol, whether or not other methods of therapy were used also. Exclusive of the seven fatal cases of embolism, in most of which death occurred too promptly to permit definite treatment, 26 of the 30 postoperative vascular complications which occurred after that date were treated with dicoumarol as the basic therapy. Three of the other four were treated by penicillin, venous ligation and paravertebral block, respectively. The fourth patient was removed to a Veterans Hospital shortly after an emergency operation for ruptured peptic ulcer and the details of the onset of the vascular lesion and of the therapy used are not known. Eight of the 26 patients treated with dicoumarol were also submitted to venous ligation and five were treated by paravertebral block. In one instance all three measures were employed.

In general, the plan of treatment was to administer 200 mg. of dicoumarol as soon as the diagnosis of phlebothrombosis or thrombophlebitis was made. Thereafter the prothrombin time of the blood was checked daily by the Quick method, and treatment was administered or withheld according to the results of this test. Twenty-seven seconds was regarded as the lower level of the effective therapeutic range and 60 seconds as the upper level of safety. The prothrombin time was kept within these limits by the administration of dicoumarol in appropriate dosages on any day on which a report of less than 40 seconds was received. These daily tests were made with the greatest care. Formerly, desiccated rabbit brain was used but recently desiccated rabbit lung has been found to be a more sensitive reagent. We have also begun to make the reports in terms of the percentage of normal activity rather than in seconds to avoid any possibility of misunderstanding on the part of the less experienced members of the resident staff.

If the prothrombin time was prolonged beyond 60 seconds, hykinone was given intravenously, in doses of 30 to 60 mg. The single instance in this series in which frank bleeding occurred was, by coincidence, the single instance in which dicoumarol was used prophylactically.

The patient, a 43-year-old white woman, had an episode of apparent thrombosis on the sixth day after vaginal hysterectomy, colporrhaphy and perineorrhaphy, 24 hours after prophylactic dicoumarol therapy had been begun. At the end of the sixth day of treatment, when the prothrombin time was 46 seconds, severe vaginal bleeding ensued. The drug was discontinued, hykinone was administered and a transfusion was given. Recovery thereafter was smooth, but 58 days later the patient re-entered the hospital with clearcut symptoms and signs, supported by roentgenologic evidence, of a pulmonary embolus, which cleared up under appropriate therapy.

It might be added that a nonfatal embolism occurred in a second case at the Vicksburg Hospital, not included in this series, 48 hours after dicoumarol therapy had been begun. The prothrombin time was only 23 seconds when the embolus became apparent.

With the exception of the hemorrhagic episode just related, patients in this series who were treated by dicoumarol recovered promptly from their vascular complications and indeed presented little cause for anxiety as soon as the prothrombin time had reached the desired therapeutic level. On the other hand, recovery was undoubtedly more rapid in the 12 cases in which anticoagulant therapy was supplemented by ligation of the femoral or saphenous vein, particularly when the clot was found and removed, and by paravertebral sympathetic block.

Thrombophlebitis was treated, in addition to the measures mentioned, by heat, elevation of the affected extremity and chemotherapy. Pulmonary embolism was treated by $\frac{1}{2}$ gr of papavarine and 1/100 gr of atropine, both being given by the intravenous route. Oxygen was given by intranasal catheter, and other measures were employed as the special case demanded. We have not employed Evans⁹ recommendation that oxygen be combined with helium and given in the form of positive pressure respiration, nor have we had any experience with prolonged continuous spinal anesthesia as recommended by Smith and Rees¹⁰.

DISCUSSION

Although this series does not reflect the policy, we are coming more and more to believe that it is the part of wisdom to institute dicoumarol therapy on or about the fifth day after operation, regardless of the smoothness of their convalescence, in patients who present the factors likely to produce vascular complications. By this time the risk of bleeding as the result of anticoagulant therapy is reduced, while most vascular complications do not occur until this time or later. The onset of these complications is usually between the fourth and the twenty-first days^{2, 6, 11}. In this series uncomplicated phlebothrombosis became evident between the fourth and fourteenth days after operation and uncomplicated thrombophlebitis between the fourteenth and twenty-second days. In 16 of the 17 cases of embolism the onset was between the fourth and fifteenth days, in 10 of these cases it was before the eleventh day. In the

remaining case, as already mentioned, it was on the sixty-fifth day after operation, following an attack of phlebothrombosis on the sixth day

Anticoagulant therapy is particularly indicated in patients over 50 years of age—in whom, however, it must be used with caution, because of possible liver damage—in patients who are markedly obese, who have malignant disease, who have varicose veins or who have a previous history of phlebothrombosis or thrombophlebitis. We use it with great caution in patients with liver damage and we regard it as contraindicated after operations on the brain or spinal cord, in the presence of a blood dyscrasia or a bleeding tendency, in pregnancy near term and in patients who require a second surgical procedure within 14 days of the first. In all such cases, vein interruption is regarded as the indicated procedure. Venous ligation and division is also considered the procedure of choice in patients who have had a nonfatal embolism. Only time will tell whether those of us who, in general, prefer anticoagulant therapy to venous ligation as the basic therapy in postoperative vascular complications are correct, or whether experienced observers as Allen and his group,¹² Evans⁹ and Zuckel,¹³ who prefer venous ligation for both prophylaxis and therapeutics, are correct in their position. Perhaps a combination of both measures will prove the answer to the problem.

Whether mass prophylaxis with anticoagulants would prevent postoperative vascular complications, or would even be justified, at the present moment seems highly debatable. In selected cases, in which difficulties are expected, the administration of dicoumarol is clearly indicated. But this form of therapy introduces a serious element of risk and if it were used routinely it might cause more deaths from hemorrhage than would be expected to occur if postoperative vascular complications were permitted to take their natural course. Moreover, it would add greatly to the burden of medical supervision, nursing and laboratory work, practical considerations which cannot be ignored in these days of shortages of physicians and nurses. The wiser plan for the present therefore seems to be to employ general prophylactic measures in all surgical cases and to limit anticoagulant prophylaxis to the special cases in which it seems indicated. DeBakey and Ochsner¹⁴ also take the position that mass prophylaxis is not the solution of the problem.

For reasons of economy, we have not routinely employed heparin at the Vicksburg Hospital, but we believe that, in spite of this objection, it ought to be administered when indicated immediately after operation and continued until dicoumarol can be substituted and the prothrombin time has reached 35 seconds. The recently published experimental studies of Kiesewetter and Shumacker¹⁵ on arterial trauma demonstrate that thrombosis is apt to occur promptly after trauma and that the most critical period from this standpoint is immediately after operation. Other studies by these same observers under controlled clinical conditions suggest that heparin combined with dicoumarol is even more effective than dicoumarol alone in the prevention of thrombosis after arterial injury and repair, and their observations seem entirely applicable to nonvascular surgery.

Embolectomy has never been attempted by us. The operation, while a theoretic possibility, is a practical impossibility. The circumstances which would make it effective simply cannot be met in practice, the chief difficulty being that if it is to have the slightest chance of success, it must be performed almost synchronously with the occurrence of the embolism. In the seven fatal cases in the Vicksburg Hospital series it would have been out of the question in four, in which death occurred between 10 and 35 minutes after the onset of symptoms, and almost impractical in a fifth, in which death occurred within three hours. The other patients lived 28 hours and seven days respectively, but neither was ever in condition to tolerate surgery of such magnitude.

This is the common experience. In a series of 78 fatal embolisms reported by Lam and Hooker⁷ from the Henry Ford Hospital, half the patients were dead within 10 minutes of the catastrophe and 75 per cent within 30 minutes. Only 10 per cent lived longer than an hour. Even theoretically, therefore, not more than 25 per cent of these patients could have been benefited by operation. An additional practical consideration mentioned by the same authors is that more than half of the emboli in their series (56 per cent) became manifest between 5 00 P M and 9 00 A M, hours when even a hospital prepared for quick emergency surgery is inevitably slower than usual in collecting equipment and personnel, particularly for an operation which is of such magnitude that it requires a surgeon of more than ordinary ability.

Since we practice early ambulation, it is ironic that one of the deaths in this series occurred in a case in which this measure could not be employed. A 65-year-old woman, somewhat anemic and with a cardiac difficulty, was submitted to radical mastectomy for malignant disease. This combination of predisposing causes strongly indicated early ambulation, but an attack of congestive glaucoma on the third day after operation made complete bed rest imperative. Death occurred on the ninth postoperative day, 35 minutes after the first symptoms of embolism became evident. In retrospect, this seems the type of case in which prophylactic dicoumarol therapy or venous ligation should have been instituted. The deceptive feature of the case was, of course, the fact that postoperative vascular complications are unusual after operations on the upper part of the body.

In this case, as in the six other fatal cases in our series, the simultaneous rise of temperature, pulse and respiration, emphasized by Allen and his associates¹ as indicative of impending pulmonary embolism, was not observed. There is no doubt of the value of this triad of symptoms and signs when it is present, but it is lacking in a large number of cases, just as it was lacking in our own series. Ochsner and DeBakey¹⁴ noted that it was absent in 12 of the 25 fatal embolism cases which they collected from the New Orleans Charity Hospital. In eight of their cases there was antecedent clinical evidence of phlebothrombosis or pulmonary infarction or of both conditions. In five other cases there was a slight rise in the pulse rate, though the temperature and respiration were unchanged. In the other 12 cases there was no symptom or sign to suggest

the impending catastrophe, and that situation is, unfortunately, in line with the general experience

SUMMARY AND CONCLUSIONS

1 The 40 cases of phlebothrombosis, thrombophlebitis and pulmonary embolism which occurred in 9,230 surgical procedures performed at the Vicksburg Hospital over a recent five-year period form a small series which is, however, typical in most respects of the clinical and other aspects of these complications. There were seven deaths in the series, all of which occurred after embolism, which came on catastrophically, without previous vascular episodes.

2 An analysis of these cases indicates the need for a careful application of general prophylactic measures after surgery and for the use of special measures in the cases in which predisposing factors exist.

3 Dicoumarol was used in 26 of the 30 cases in this series which occurred after June 1, 1944, exclusive of the seven fatal cases of embolism, in none of which anticoagulant therapy was employed. Experience suggests that recovery is prompter if venous ligation or sympathetic block is employed in combination with dicoumarol.

4 Prophylactic anticoagulant therapy, possibly a combination of heparin and dicoumarol, is probably indicated in selected cases, but mass prophylaxis by this means would introduce more problems than it would solve.

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DISCUSSION—DR ROY D McCLURE, Detroit Through the years it seems that the deepest scars that have been left on most of us as surgeons have been the results of post-operative deaths that should not have happened I felt in 1911, while working with Dr Eugene Poole at the New York Hospital, that massage and early exercise in bed would reduce the number of thromboses and fatal embolisms Then, while Doctor Halsted's resident at Johns Hopkins Hospital, I saw in five weeks on his service and that of Dr Howard Kelly five deaths from embolism We talked with Dr J J Abel and Dr William Howell about the possible use of hirudin but that proved to be too dangerous When Doctor McLean, working on anticoagulants in Howell's laboratory, brought out heparin in 1916, we used it immediately after that in Detroit The reactions, however, due to impurities, were so terrible in three cases that we never even reported it It was not until about 1937 that the group in Toronto put out a purified heparin which was safe to use We started using that in all cases which showed beginning pain in the calf of the leg In spite of that we had in 1938 five deaths from embolism, four in 1940, five in 1941, three in 1942, five in 1943, eight in 1944 and 1945 However, that was in about 900 operations a month so it was not a large percentage, but we felt that these deaths should not have occurred With the exception of two, not one of these fatal cases had specific treatment, the fatal cases came just as a bolt out of the blue

The question is, how can we determine which patients will have thrombosis and pulmonary embolism First of all, we agree absolutely with Doctor Parsons that age helps somewhat in predicting In our series the occurrence is almost unknown under the age of 30 Certain types of operations, as he said, seem more prone to be followed by embolism Gastrectomy, for example, led our list with 1.06 per cent deaths from fatal embolism, followed by colon and gallbladder operations and prostate operations, etc

At the present time we have our residents watch very carefully the temperature chart and the calves of the patient's legs, during the postoperative period An unexplained fever may lead to the giving of anticoagulants, on suspicion The finding of a positive Homan's sign indicates to us immediately either a femoral ligation at the indicated site, or anticoagulant therapy, or possibly both We give heparin immediately after operation We used to give it preoperatively, but we had a few hemorrhages in the wound and gave that up It takes about two days to get a positive effect from dicumarol I speak knowingly because I myself have been taking it daily for ten months What we have all hoped for was that someone would show us a test which would indicate to us an impending thrombosis and which would anticipate all the clinical signs just mentioned Such a test was hopefully reported at the meeting of the American Surgical Association in Quebec last May by Mahoney and his associates* Perhaps Doctor Morton can tell us of their subsequent experience

They believe they have demonstrated the value of daily prothrombin times during the postoperative period, and if that time went down they would start anticoagulants When I returned to Detroit from that meeting I was very enthusiastic about this and asked Doctor Barron and Doctor Lam of our staff to start this method immediately to see if we could anticipate which patients would have thrombosis and embolism To date we have studied 179 cases Each patient has eight prothrombin tests, one the day before operation, two the day of operation, and then one each day following operation for five consecutive days Of the 179 cases, six have shown leg thrombosis without infarction, four have shown high prothrombin levels, but in two there was no elevated prothrombin as a warning I feel sure our prothrombin estimations are well done Seven patients had clinical phlebothrombosis of the lower extremity and also non-fatal pulmonary infarcts

* Prothrombin Activity, Rachel S Sandrock, M D, and Earle B Mahoney, M D, Annals of Surgery, Sept 1948, Vol 128, No 3

In only two of these did the prothrombin curve give a warning, the other five showed perfectly straight prothrombin curves. One patient had a coronary occlusion during the study. His prothrombin curve gave no warning. As you know, the American Heart Association feels that in coronary thrombosis dicumarol has been a great aid in cutting down the number of deaths.

Of the patients who had had no clinical evidence of thrombosis, 64 had so-called elevation of prothrombin level and 98 were negative. We cannot say for certain that the 64 positives had no thrombosis, but they were not treated, and we have no reason to regret that we did not start anticoagulant therapy on them.

In summary, we have not been able to corroborate the findings of Mahoney and his associates that daily prothrombin determinations are of great value in predicting thrombotic complications, but further studies along this line are strongly indicated.

DR GEORGE T. MCCUTCHEN, Columbia, S. C. I would like to recite an experience that lends emphasis to Doctor Paisson's idea that it is well in some cases, particularly in those in whom you suspect embolism is likely to occur, to give some type of prophylactic medication. A little more than a year ago I encountered a patient who started with a primary disease in his chest. He was seen by his physician, X-ray films were taken, his clinical manifestations were similar to those of a small pulmonary embolus. He had pain in the chest and coughing of blood, but embolus was not suspected at the time. About two days later, on further questioning, it was found that he had had some soreness of his leg, in the calf, for three or four days prior to onset of symptoms.

On examination of the leg it was found that he had a positive Homan's sign, some swelling and tenseness of the calf. Ligation of the femoral vein was done and a clot was found at the point of ligation. During the next three or four months I encountered two other cases of a similar nature and was completely puzzled by the problem. I wrote to Dr. Mims Gage and Dr. Alton Ochsner, and they told me that so far as they knew this particular thing was unique, that they had never heard of it. Since that time there has been a total of seven patients with a similar syndrome, all in patients who had had no bed rest and in whom the leg had not been subject to trauma. We had to call in a term for it, and picked out one that rolled off the tongue very easily—spontaneous unprovoked phlebothrombosis. The last patient we saw might be questionable to some extent, a boy aged 15 who had had an appendectomy some five weeks before. He was ambulated immediately and had a completely uneventful convalescence. Nine weeks later, as he was entering an elevator, he was suddenly seized with pain in the chest and severe cough, and it was discovered that he had physical and X-ray indications of a pulmonary embolism, with pain, tenderness and swelling of the calf. That was the only one of the number who had, in recent weeks at least, been confined to bed.

It brings up an important point in diagnosis for our fellow internists as to some obscure conditions of the chest, and I wonder how often it might happen in cases of sudden death. None of these patients died, all had emboli of rather mild nature. We are completely at a loss as to the explanation of the cause of phlebothrombosis, I believe. Certainly we have to scratch our heads or stretch a point to believe that bed rest or trauma has much to do with it. So far as I am concerned it is still an imponderable problem, and one which is a long way from solution, and I believe it falls within the realm of the biochemist and the physiologist to produce the answer. I don't believe surgeons can. All these patients were subjected to elaborate study of the clotting mechanism and no abnormalities could be found. It remains for more delicate tests to be developed, or to find factors other than those we now understand as being causative in phlebothrombosis.

DR. FREDERIC W. BANCROFT, New York. Our experience with the tests for phlebothrombosis has been a good deal different from that of Doctor McClure. Doctor Stanley-Brown and I started this study in 1928, and at that time we made more than 4000 tests routinely on our surgical cases. It may be that the reason our results showed more was because at that time we did both prothrombin and fibrinogen tests, but in the series

we studied we had only one case, a breast amputation, done at another hospital, where there was no elevation of the clotting factors. The others had either high prothrombin or fibrinogen, and in the cases that developed accidents on routine study they had had warning signs before. So I do feel that we may find some method to ascertain which are the dangerous cases.

I was interested in Doctor Parsons' statement about the high percentage in hysterectomies. I think we have here possibly a different picture than in operations above the pelvis. I wish to report one case that illustrates what I mean. A woman had had a cesarean operation, a perfectly normal postoperative temperature, she had gone home, and on the tenth day afterward she had pain in the chest. She was brought back to the hospital and on X-ray it was a question as to whether it was an infarct or a virus pneumonia. Her legs were carefully measured, there was no tenderness and no swelling. However, seven days after onset of the pain in the chest, she had evidence of phlebotrombosis in the right thigh. I operated on her and took out the thrombus, but did not have a satisfactory suction apparatus, so did not feel that I had gotten entirely above the thrombosis. However, she apparently improved, but at the end of eight days after this she had pain in the chest again, and the X-ray showed an infarct in the opposite chest, seven days later she showed obvious thrombosis on the right. I operated on that side and she was given spinal anesthesia which I think was a mistake, because in flexing her forward I think they liberated another thrombus, anyway she died. It was obvious from the postmortem that the thrombosis had occurred primarily in the pelvic vein and had proceeded in a retrograde manner down her thigh.

A similar case is that of a woman who had had a normal delivery, and on the seventh postoperative day had pain in the chest, and X-ray evidence of pulmonary infarct—no evidence in the thigh. We went in simultaneously on both femoral veins, they were in spasm and did not contain a clot, but in passing a suction tube up to near the bifurcation of the vena cava we got clots from both sides and with anticoagulant therapy she went home five days later.

I think it is a difficult thing to know whether or not to use anticoagulants, or operation. I have done 35 thrombectomies, where the thrombus has extended above the femoral ligament. That one case is the only case of death, the rest have recovered satisfactorily. I have also given anticoagulants. I have not operated on any patient who had had a thrombosis for about ten days before being seen by me because I felt if they had thrown no embolus by that time, they were not going to, and that they could be treated by lumbar sympathetic block. I would like to say one word about our concept of early ambulation. Many of us have thought that if we got patients up and let them sit in a chair we were giving early ambulation. As a matter of fact that is the worst position we could possibly put them in for venostasis. The feet are much lower than they are in a Gatch bed, the knees are over the edge of the chair where there is compression on the popliteal veins, and there is sharp flexion of Poupert's ligament—all factors, I think, that aid venostasis. It is my idea that early ambulation is to get a patient out of bed, make him walk around the bed, get back into bed and lie flat, and not sit part of the time in a chair in as poor a position, probably, as we can get.

I wish to thank Doctor Parsons, and I enjoyed his paper very much.

DR HUGH A. GAMBLE, Greenville, Miss. In the discussion of Doctor Parsons' paper there has been little said about the prophylaxis of postoperative phlebitis or thrombophlebitis. In 1934 I published in the American Journal of Surgery a description of what I called a bedcycle and later, in discussing a paper before this Association, described our method of preventing thrombophlebitis. Up to that time we were losing about one case out of every 1500 operations from pulmonary embolism. We had what seemed to be an epidemic of thrombophlebitis. A large proportion, at least one-third or one-fourth of the operative cases, would develop the condition and this began to be so much the case that patients in coming to the hospital would inquire as to what caused it and if there was any way to prevent it.

We went over the medical literature for the preceding 40 years. We found that Aschoff gave the most lucid description of the pathogenesis of this condition that we had seen. Adopting Aschoff's theory as to the causation of thrombophlebitis we had built what has been called a bedcycle. It is simply two bicycle pedals mounted upon a frame so that it can be placed upon the bed, and the patient is required to exercise his lower extremities on it for a period of five minutes twice a day, beginning the day of operation. While we felt that this was of extreme importance, we realized that during and following operation there is marked concentration of the blood, there is marked increase in the clotting elements present, and that it is at this time that the venous flow is at its lowest level. Therefore, we made it a practice of giving intravenous glucose in 5 per cent solution continuously through operations in an endeavor to maintain blood water levels. In order to promote the flow of venous blood we have routinely, for the first 24 hours following operation, required that these patients be given inhalations of carbon dioxide and oxygen every three hours for three minutes. Later on we began to get them up early, usually, where practicable, within the first 24 hours, requiring them to walk around the room. However, regardless of this we have maintained the use of the bedcycle throughout the whole period of hospitalization.

Since 1933 my brother and I have had something over 52,000 major operative cases. We have had one death from pulmonary embolism during this time. We have had seven cases of thrombophlebitis and I cannot but feel that these preventive measures have been effective in lowering the incidence of this condition.

The one death I speak of occurred in a man on the 21st day following operation. He had had a resection of the large bowel for carcinoma of the ascending colon and an end-to-side ileo-colostomy. He had had no symptoms suggestive of phlebitis of the lower extremities, but on that day he complained of pain in his lower abdomen and thought that he had eaten something that had disagreed with him. He was given an enema but was not entirely relieved of discomfort. At four o'clock in the morning of the 21st day I was called to see him and when I reached the hospital found him dead. An autopsy showed a large embolus in the right pulmonary artery, which had originated in the veins draining the transverse colon.

I feel that there is not enough attention paid to the fact that these embolic processes begin immediately after operation when the blood is at its highest concentration and the venous flow is at its lowest level and that, if you employ measures that will keep the water level of the blood up to normal and promote the flow of blood from the outset and keep it up from day to day, you will be convinced of the efficaciousness of this method of preventing these complications, which in some sections of the country seem to be so prevalent.

DR ROY C WIGGINTON, Vicksburg (closing). We would like to thank those who have so kindly and so generously discussed our paper. We, of course, do not believe that either anticoagulant therapy or vein interruption represent necessarily the final answer as to the therapy of venous thrombosis. We do believe, however, that perhaps careful evaluation of the risk in each surgical patient, determined by the criteria based upon the experiences of many who have studied the problem, will indicate those patients who should have dicoumarol as a prophylactic measure. We believe that the intelligent use of dicoumarol in this fashion might perhaps greatly reduce the mortality and morbidity incident to venous thrombosis, and might do so without posing impossible laboratory problems or unduly endangering lives.

At the Tulane University, and I believe at other places both in America and abroad, a great deal of work is now being done on the mechanism of blood clotting. At least two previously unknown factors have been discovered. As a result of this study many of the previous theories pertaining to blood coagulation may perhaps be discarded. It is further possible that those now investigating this phase of the subject may eventually solve the problem. Certainly, at the moment, its solution is by no means complete.

COMPARISON OF EFFECTIVENESS OF NEWER ANTIBIOTICS IN EXPERIMENTAL PERITONITIS A PRELIMINARY REPORT*

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SINCE THE DISCOVERY of penicillin and streptomycin, other antibiotics are in the process of being studied and developed. Of the new group, chloromycetin and aureomycin are representative of types that should prove to be of value in certain surgical conditions.

Chloromycetin,[†] which is obtained from filtrates of submerged aerated cultures of a *Streptomyces* sp., has been found to be quite effective against a number of rickettsiae, and several gram-negative bacteria. It was originally prepared by Ehrlich and associates from liquid cultures of a *Streptomyces* first isolated by Burkholder and shown by him to possess antibacterial activity. The crystalline substance is relatively insoluble in water, but well absorbed from the gastro-intestinal tract. It is well tolerated when given orally and serum levels of the drug after oral administration have been found to parallel those after parenteral injection. Its toxicity is apparently low.

In vitro, crystalline chloromycetin has been found to be inactive against yeasts and filamentous fungi, inactive against protozoa, moderately active against gram-positive bacteria and *Mycobacterium tuberculosis*, and active against gram-negative bacteria and *Borrelia recurrentis*. After single doses in the dog, only small amounts of antibacterial substances are excreted in the urine, indicating inactivation in the body and perhaps excretion by other routes.

Woodward⁵ has demonstrated its clinical importance and significant chemotherapeutic effects in the treatment of typhoid fever. Pincoffs⁶ recently reported its effectiveness in the treatment of Rocky Mountain spotted fever.

Aureomycin,[‡] which is derived from a strain of *Streptomyces aureofaciens*, has been shown to possess, in vitro, antibacterial activity against numerous gram-positive and gram-negative bacteria.

It appears to be bacteriostatic, rather than bactericidal, except in high drug concentration. In experimental studies, no significant concentrations were obtained in blood serum more than 25 hours after the last injection was given, with a dosage rate of 20 mg per Kg of body weight, twice a day for ten days. Bryer⁸ has reported that when aureomycin was administered orally to a 150-

* Read before the Southern Surgical Association, White Sulphur Springs, W Va., December 8, 1948.

† The chloromycetin used in this study was supplied by Parke, Davis & Company.

‡ The aureomycin used in this study was supplied by the Lederle Laboratories Division, American Cyanamid Company.

pound (about 68 Kg) man in doses of 500 mg twice a day and 40 mg intramuscularly every six hours, blood levels of 0.6 to 2.4 micrograms per milliliter of serum were observed one hour after an injection was given. The antibiotic produced a greenish-yellow discoloration of the urine, in which concentrations of 40 to 80 micrograms per milliliter were observed. He also reports that infections of the urinary tract due to coli aerogenes and *S. faecalis* have been sterilized and evidence of inflammation has disappeared when patients were treated with aureomycin by mouth.

It was thought that the properties of chloromycetin and aureomycin should render them valuable agents in the treatment of acute diffuse peritonitis due to mixed infections with both gram-positive and gram-negative bacteria.

Murphy *et al*¹ have demonstrated that streptomycin hydrochloride injected intramuscularly will not only pass into the peritoneal cavity of normal dogs, but that the concentration of the drug in the peritoneal fluid may surpass the concentration in the blood.

Although there is a satisfactory test for the determination of chloromycetin levels, there is no comparable dependable test for evaluation of aureomycin levels. Aureomycin is quite unstable and additional study will be required in order to develop an accurate method of determining its levels in body fluids. In this study, no attempt was made to determine tissue fluid levels attained with the antibiotics studied.

The technic used to produce peritonitis in this study is one which was introduced by Bowe and co-workers³ and modified by Fauley and his associates⁴. Steinberg and Martin¹⁰ have shown that a peritoneal infection diffuses throughout the peritoneal cavity fairly promptly after perforation of the bowel takes place. In their study of experimental peritonitis, they concluded that perforation of the gangrenous cecal wall was due to increased pressure, and could be produced by the instillation of air as successfully as when castor oil was used. A technic described by Silvani¹² for producing fulminating diffuse peritonitis was not considered applicable to this study.

TECHNIC

Animals were selected at random from stray, mongrel adult dogs, weighing from 15 to 20 pounds and excluding pregnant dogs, and dogs previously operated upon. The abdomen was shaved, scrubbed and painted with iodine and alcohol. Aseptic technic was rigidly observed. Under intravenous Nembutal Sodium anesthesia, the abdomen was entered through a right rectus incision and the appendix drawn into the wound. Mesenteric attachments were divided, and the appendiceal vessels were clamped, divided and ligated with silk. In order to minimize a tendency toward intussusception, the appendix was ligated 1 cm from its base, with three coarse silk ties, rather than directly at its base (Fig. 1). The distal half of the appendix was then traumatized with a crushing clamp, the viscera replaced, and the incision closed in layers with silk. No drains were used and no dressings applied. Immediately after operation, each animal received 500 cc of castor oil by stomach tube.

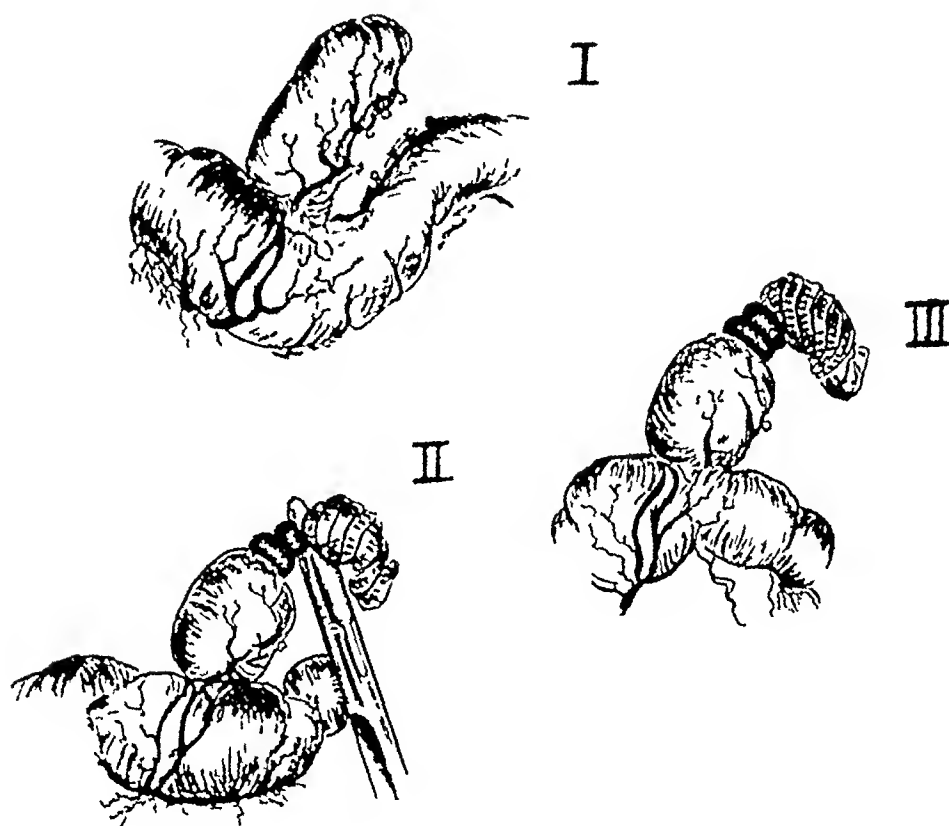


FIG 1—Technic for producing experimental peritonitis in dogs (I) Dissection of stump and ligation of mesenteric attachments (II) Crushing of distal end (III) Ligation with three strands of heavy silk Ligation for diagrammatic purposes is further away from the base than actually practiced

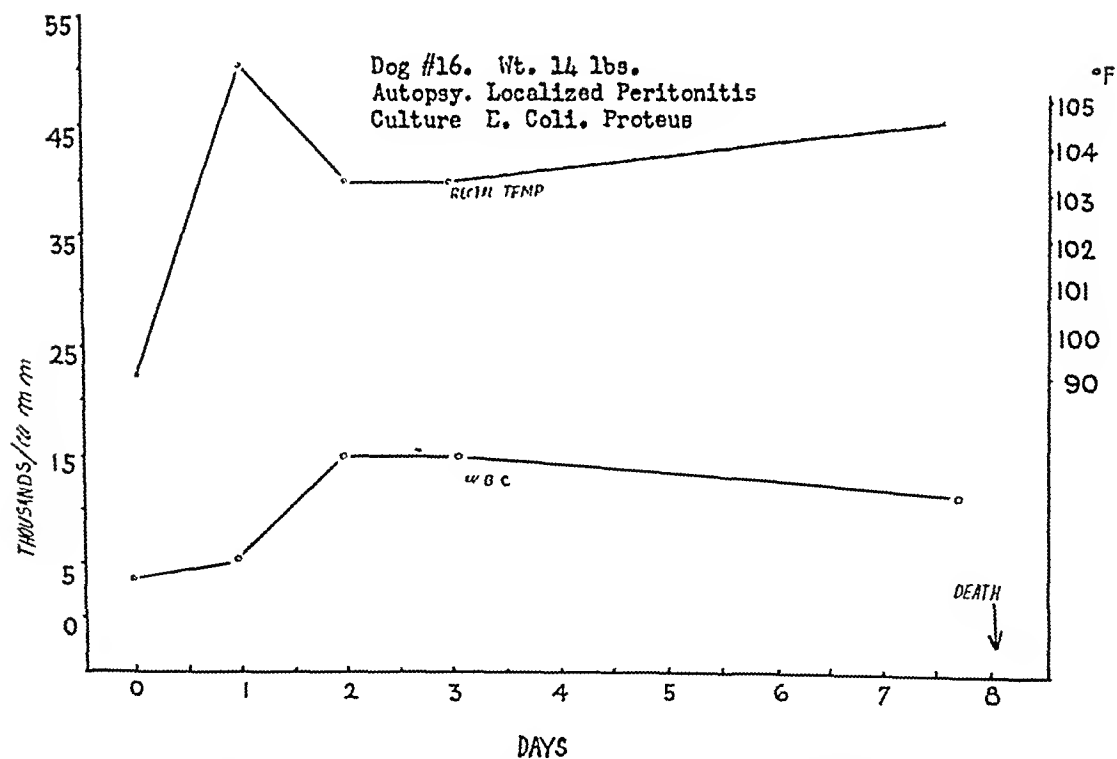


FIG 2—Typical course of control animal dying on the eighth postoperative day Note sharp rise of temperature during the first 24 hours postoperatively Minimum temperature (R) postoperatively, 103°F with leukocytosis of 15,000

No attempt was made to withhold food or water postoperatively, and no intravenous fluids were given. Temperature and leukocyte counts were determined every other day. Necropsy was performed on all fatalities shortly after death. All animals operated on are included in the series. The animals that survived were examined not earlier than 14 days after operation. Culture studies were made of peritoneal exudate in all animals.

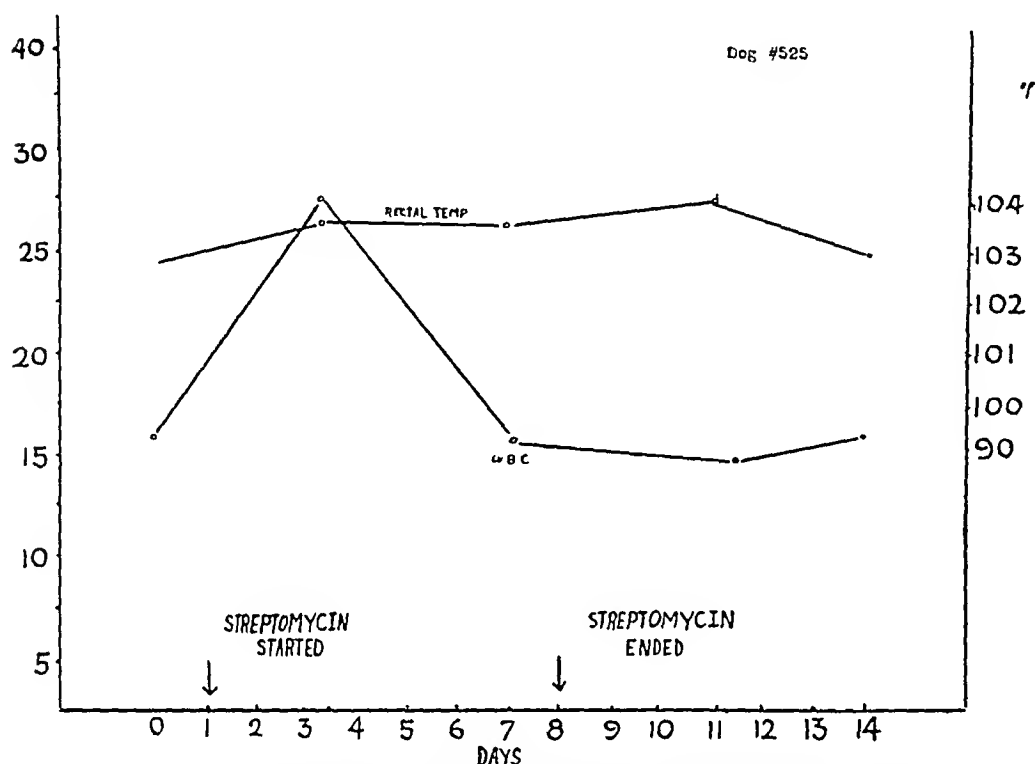


FIG 3—Typical postoperative course of dog treated with streptomycin. Maximum temperature (R) 104°F with leukocytosis that became elevated to 28,000.

Although it is recognized that in peritonitis, penicillin probably enhances the effectiveness of streptomycin, and vice versa, it was not combined with any of the antibiotics studied.

Ten animals were used as controls. Of these, eight died of acute diffuse peritonitis, six of them within the first four days. Two animals recovered, a survival rate of 20 per cent (Fig 2).

Ten animals were treated with streptomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 75 mg every six hours intramuscularly, a dosage equivalent of 300 mg every 24 hours. Of these, four died of peritonitis, three of them within the first six days. Six animals recovered, a survival rate of 60 per cent (Fig 3).

Ten animals were treated with aureomycin, starting 24 hours postoperatively and continuing for eight days. The dosage was 100 mg four times a day orally. Of these, only one animal died, this occurring as late as the ninth day. Nine animals recovered, a survival rate of 90 per cent (Fig 4).

COMPARISON OF NEWER ANTIBIOTICS IN PERITONITIS

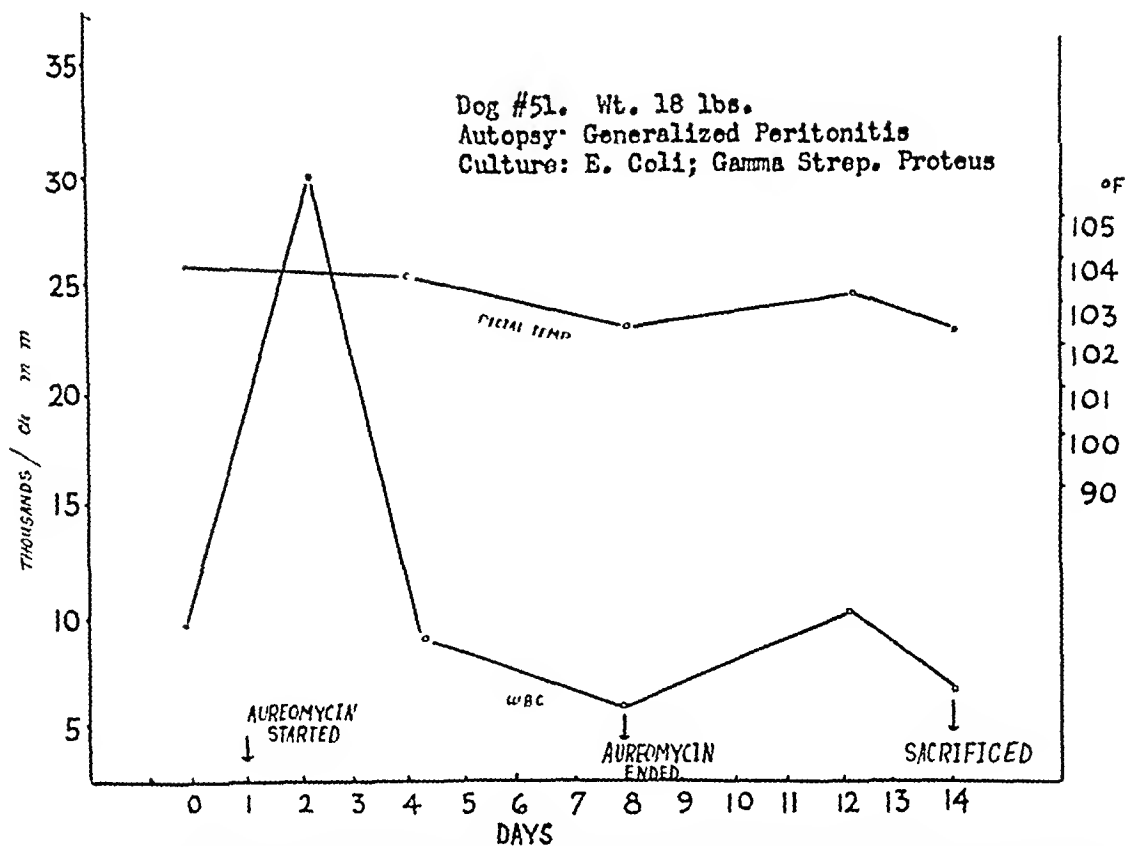


FIG 4—Typical postoperative course of dog treated with aureomycin Maximum temperature (R) 103°F with sharp rise of leukocytosis to 30,000 and dropping to within normal limits on the fourth postoperative day

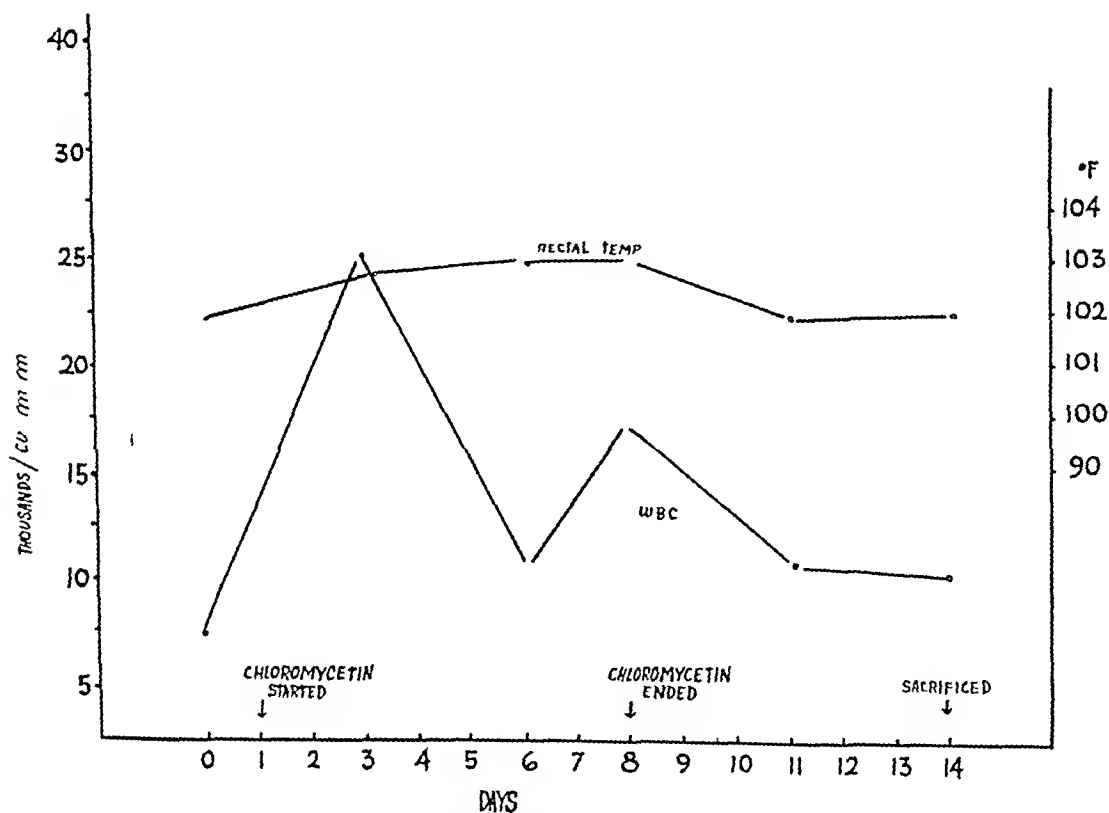


FIG 5—Typical postoperative course of dog treated with chloromycetin Maximum temperature (R) was 103°F with leukocytosis of 25,000

Unfortunately, at the time of this study, chloromycetin was not available in sufficient quantity for a fair comparison with the above observations. However, the animals in which it was used survived with an initial oral dose of .25 Gm followed by .062 Gm every three hours. A larger series of animals are to be studied with chloromycetin therapy for more effective evaluation (Fig 5).

All animals were autopsied as soon after death as possible, and peritoneal exudate culture studies made. In addition, all dogs that survived 14 days were sacrificed and culture studies made (Table I). Five control animals showed a predominance of *Escherichia coli*. Eight animals treated with streptomycin

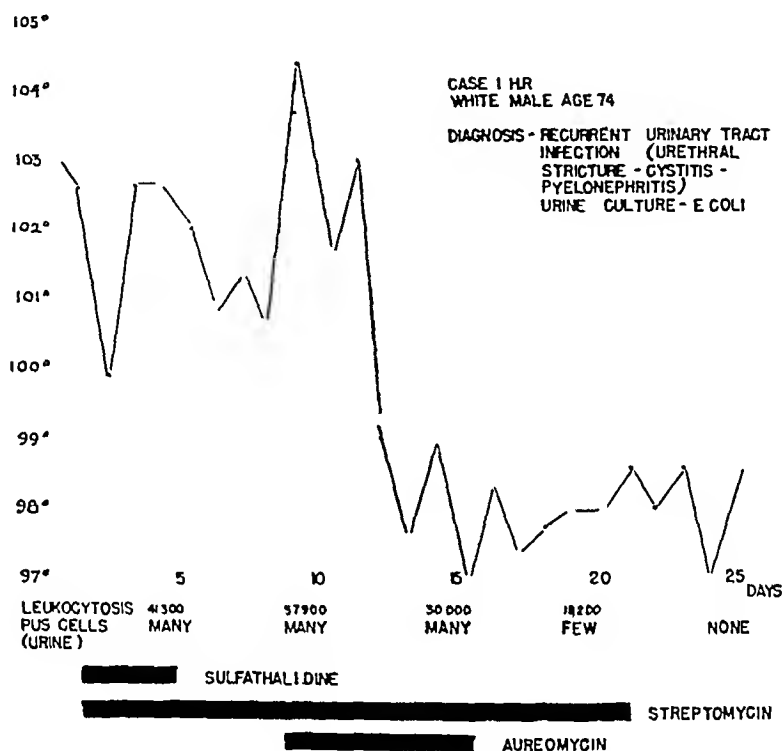


FIG 6—Clinical course of Case 1, H R Urinary tract infection with *Escherichia coli*. Following treatment with aureomycin, urine became culture free. Patient expired of a massive gastric hemorrhage after being ambulant and ready for discharge.

showed *Escherichia coli*, while only four treated with aureomycin showed this organism. It is interesting to note that of ten animals treated with aureomycin, eight showed various types of proteus organisms.

The comparative survival rates are shown in Table II.

CLINICAL STUDIES

Two patients with infections of the urinary tract due to *Escherichia coli* and two patients with a generalized peritonitis were treated with aureomycin with favorable responses.

Case 1—H R, No 17022 White male, age 74, admitted to the University Hospital on September 15, 1948, with a complaint of pain in the legs and back associated with chills.

and fever Three months previously, he had been discharged from the hospital following a transurethral resection for benign prostatic hypertrophy At the time of his previous admission, in addition to a benign prostatic hypertrophy, additional diagnoses of gastric ulcer, cystitis and pyelonephritis were made

Admission specimen of catheterized urine, in addition to showing innumerable white blood cells, subsequently cultured *Escherichia coli* (Fig 6) Temperature on admission was 103.2°F He was immediately placed on 1 Gm of sulfathalidine every six hours and 250,000 units of streptomycin every three hours Sulfathalidine was discontinued after four days Streptomycin was continued at the same dosage level Urine cultures one week after admission continued to show *Escherichia coli* and *Pseudomonas pyocyanea* His

TABLE I—Incidence of Bacteria Cultures from Peritoneal Exudate of Dogs with Experimental Peritonitis^a

Organism	Controls (10 Dogs)	Streptomycin (10 Dogs)	Aureomycin (10 Dogs)	Chloromycetin (1 Dog)
<i>Escherichia coli</i>	5	8	4	1
<i>Gamma streptococcus</i>	4	5	3	0
<i>Proteus</i>	4	2	8	1
<i>Clostridium perfringens</i>	5	3	1	1
<i>Staphylococcus albus</i>	4	0	0	0
<i>Streptococcus viridans</i>	0	2	0	0
Beta hemolytic streptococcus	1	2	0	0
<i>Staphylococcus aureus</i>	2	0	0	0

^a Note that *Escherichia coli* was cultured from eight of ten dogs treated with streptomycin while eight of ten dogs treated with aureomycin cultured various proteus organisms

course remained septic and extremely stormy On September 23, 1948, or eight days after admission, his temperature rose to 104.4°F He was placed on an oral dose of 1 Gm of aureomycin every six hours for two days, following which the dosage was reduced to 0.5 Gm every six hours His temperature returned to normal in two days and he showed dramatic improvement

Five days after starting aureomycin therapy, the urine became clear of white blood cells, and cultures were negative After six days, aureomycin therapy was discontinued,

TABLE II—Comparison of the Survival Rate in the Treated and Untreated Animals^a

	No. Dogs	2 Days	Survived 4 Days	8 Days	14 Days
Controls	10	8	6	4	2
Streptomycin	10	10	8	6	6
Aureomycin	10	10	10	10	9
Chloromycetin	1	1	1	1	1

^a Note that 90 per cent of the dogs treated with aureomycin survived, and 60 per cent of the dogs treated with streptomycin Only 20 per cent of the control dogs survived

following which urine cultures again became positive However, despite this, his leukocytosis decreased, and his temperature remained normal He became asymptomatic and had been ambulant when he suddenly succumbed to a massive gastric hemorrhage Subsequent autopsy revealed, in addition to a bilateral hydronephrosis, a benign gastric ulcer

Case 2—J. P., No. 26677 White male, age 72, admitted to the University Hospital with a diagnosis of recurrent carcinoma of the bladder On August 16, 1948, a bilateral transplantation of the ureters into the sigmoid was performed Postoperatively, he was placed on sulfathalidine 1 Gm every four hours, and also 50,000 units of penicillin every four hours (Fig. 7)

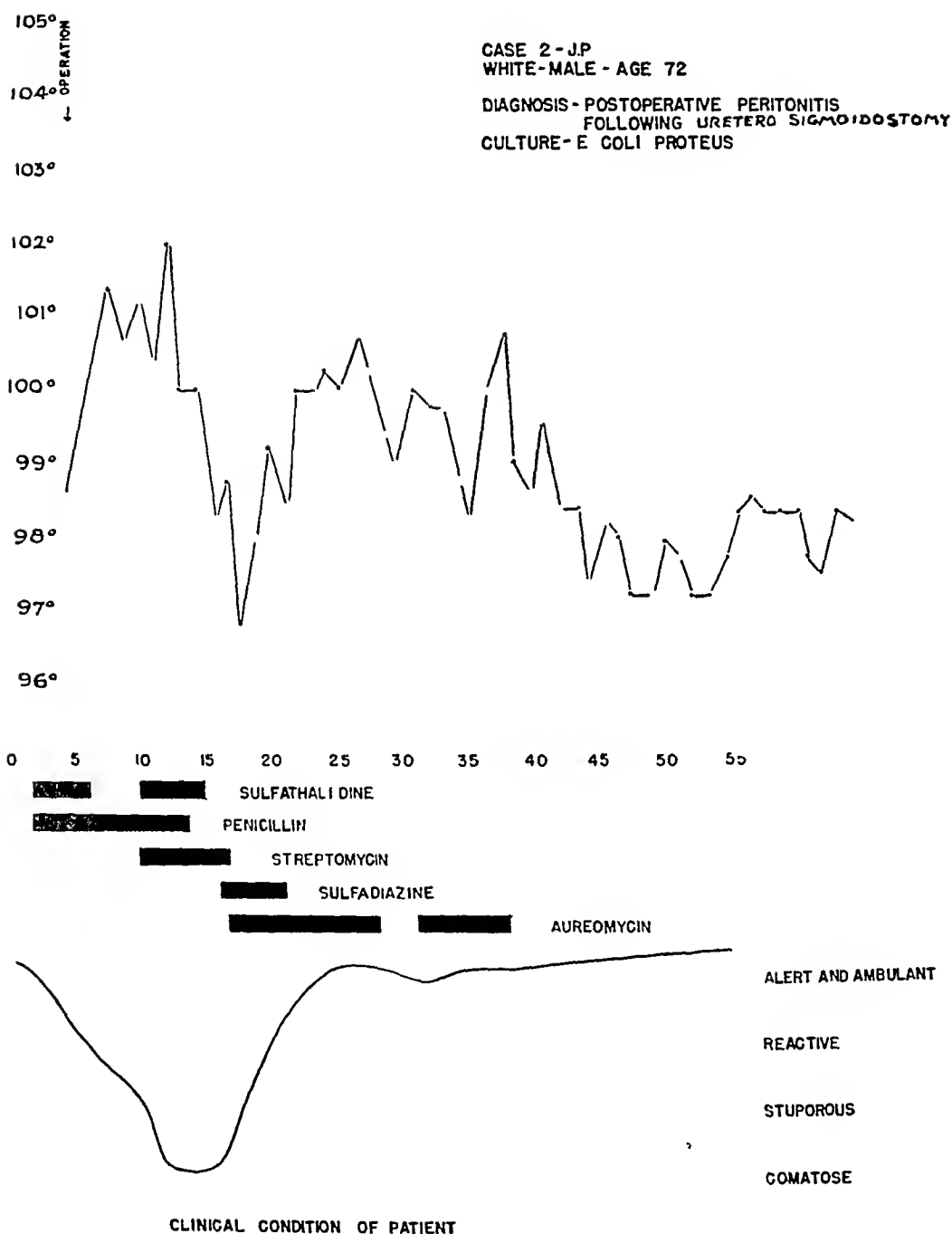


FIG 7—Clinical course of Case 2, J. P. Urinary tract infection with *Escherichia coli* and *Proteus* organisms. This patient was treated with sulfathalidine, penicillin, streptomycin and sulfadiazine in the order named. Aureomycin was started on his 15th postoperative day and two days before streptomycin was discontinued. Preceding the administration of aureomycin, he was comatose. Within 24 hours he showed marked response and within seven days after starting aureomycin, he was ambulant.

He developed evidence of a generalized peritonitis. A moderate dehiscence occurred and the incision drained copious quantities of foul smelling pus, which cultured *Escherichia coli*.

He was placed on 250,000 units of streptomycin every three hours, which was discontinued after one week when he failed to show improvement. Two days before discontinuing streptomycin, he was placed on 3 Gm of sulfadiazine intravenously every day. After five days, sulfadiazine therapy was discontinued. When streptomycin was discontinued, he was placed on aureomycin 300 mg intramuscularly every six hours. The dosage variation is shown in Figure 7. After sulfadiazine was discontinued, aureomycin was the only specific therapy given.

Preceding the administration of aureomycin, he had been comatose. Within 24 hours he showed marked response, and within 7 days his general condition had improved sufficiently to permit ambulation. Aureomycin therapy was discontinued after the twelfth day. Cultures of the abdominal wound at that time revealed a heavy growth of *Proteus vulgaris*.

Several days after discontinuing aureomycin, wound drainage increased and cultures showed a return of *Escherichia coli*. He was again placed on aureomycin. He improved immediately. He was discharged from the hospital on his 39th day, or 25 days after starting aureomycin therapy.

COMMENT It is conceivable that when aureomycin was first discontinued and wound cultures showed a heavy growth of proteus organisms, chloromycetin might have been of value. In vitro, aureomycin is not effective against proteus organisms while chloromycetin is quite effective.

The dramatic and speedy improvement upon the administration of aureomycin suggests a rapid control of toxins elaborated by the offending organisms, and recognized to be an important factor in the lethal effect of peritonitis.

Case 3—H O, No 42236. Colored male, age 48, admitted to the University Hospital with a history of right lower abdominal pain, and vomiting of three days duration. A diagnosis of acute appendicitis with peritonitis was made. At operation, a gangrenous and perforated appendix was removed. The peritoneal cavity contained free, foul smelling turbid fluid, which, when cultured, yielded *Escherichia coli*.

Postoperatively, he was given 100,000 units of penicillin every two hours for two days, and afterwards 100,000 units every three hours. He was also given, intramuscularly, 40 mg of aureomycin, in a buffer solution, every four hours. The dosage was varied as shown in Figure 8 until on the sixth postoperative day he was given 250 mg of aureomycin orally every six hours.

His entire postoperative course was remarkably uneventful, and on the 15th day he was discharged from the hospital.

Case 4—W G, No 18949. White male, age 39, admitted to the University Hospital with a history of pain in the right lower abdomen of one week's duration, not associated with nausea or vomiting. Admission temperature was 104°F. The abdomen showed a board-like rigidity. Diagnosis of generalized peritonitis was made. At operation, a gangrenous, perforated appendix was removed. Fecal material was found lying free in the peritoneal cavity. A generalized, loculated type of peritonitis was also found, with thick exudate. The pelvis was filled with pus. Fluid culture, which was foul smelling, yielded *Escherichia coli*. The abdominal cavity was drained.

Postoperatively, he was placed on 50,000 units of penicillin every three hours, and 500 mg of aureomycin, orally, every four hours for five days. After five days, the same dosage level was continued every six hours instead of every four hours.

He was discharged from the hospital on his 14th postoperative day, asymptomatic and incision healed.

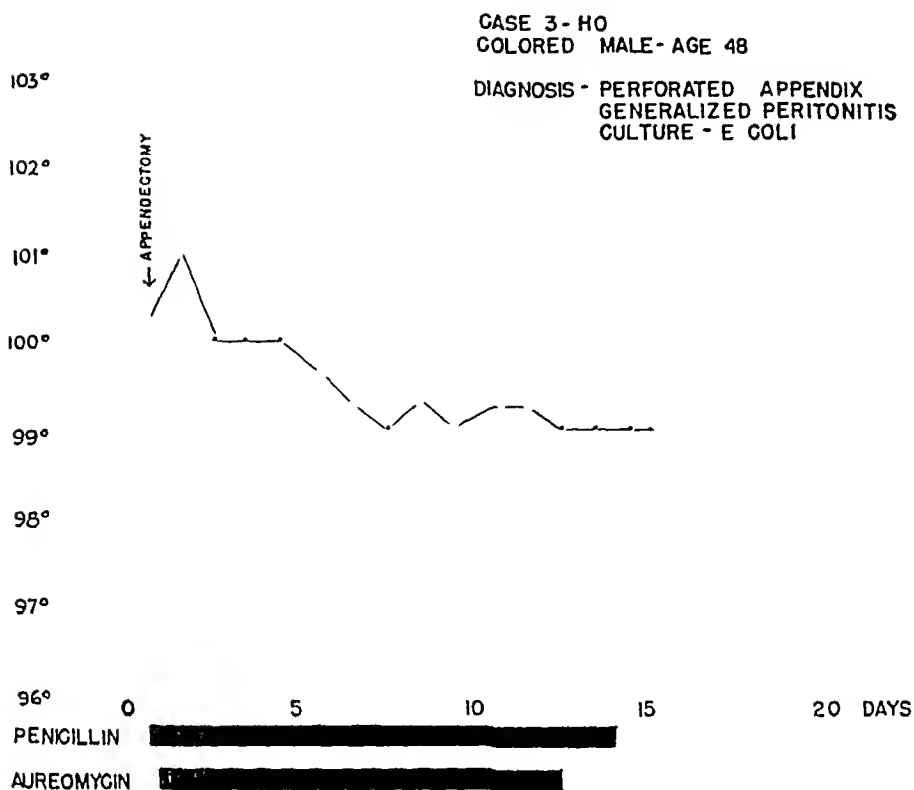


FIG 8—Clinical course of Case 3, H O with generalized peritonitis and cultured *Escherichia coli*. Patient treated with penicillin and aureomycin

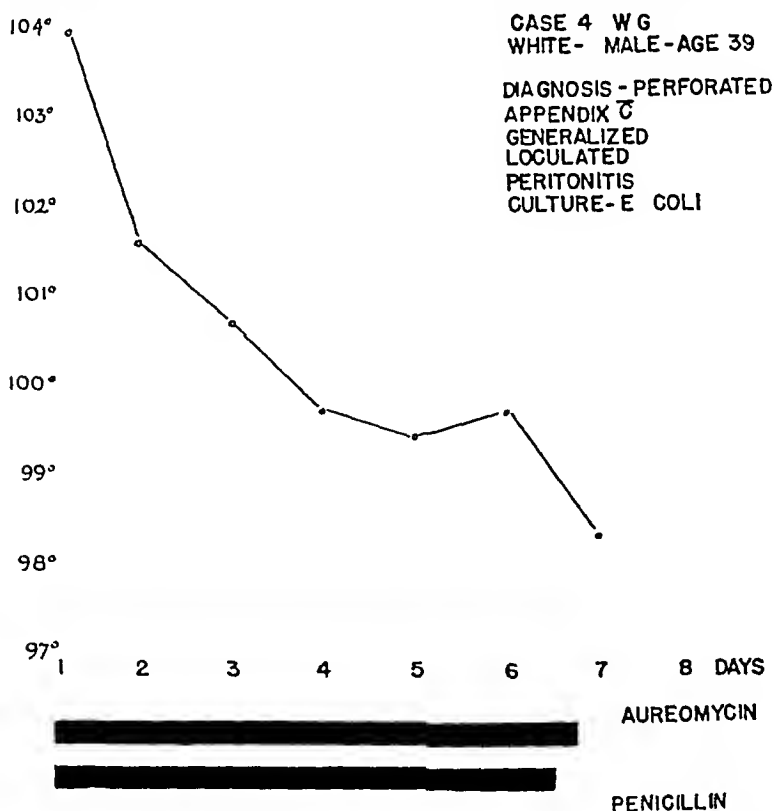


FIG 9—Clinical course of Case 4, W G with generalized peritonitis and cultured *Escherichia coli*. Patient treated with penicillin and aureomycin

SUMMARY AND CONCLUSIONS

- 1 Experimental peritonitis has been produced in a series of dogs in an attempt to compare the protective significance of streptomycin and aureomycin
- 2 The survival rate of the control animals was 20 per cent as compared with a survival rate of 60 per cent for those treated with streptomycin and 90 per cent for the dogs treated with aureomycin
- 3 Chloromycetin shows suggestive evidence that it may have comparable value in peritonitis
- 4 Two patients with *Escherichia coli* infection of the urinary tract and two patients with generalized peritonitis were treated with aureomycin with apparently favorable results
- 5 Observations of other workers suggest that the major field of usefulness of aureomycin may be in the treatment of infections with rickettsia and certain of the virus group. The results noted in the present study warrant more extensive observations of its effects in a variety of bacterial infections

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DISCUSSION—DR C HAL INGRAM, Baltimore I would like to say just a word concerning the technic that we used in producing peritonitis in experimental animals. Adult, mongrel dogs, weighing between 15 and 20 pounds, were used. All operations were done through a right rectus incision, observing aseptic technic.

The appendix was delivered into the wound, the meso-appendix was divided, and the blood supply to the appendix was carefully ligated with silk. The appendix was then triply ligated with coarse heavy silk about one centimeter from its base. After ligating the appendix it was crushed distally with an appendiceal crusher, hoping to cause necrosis. Following this the appendix was allowed to fall back into the peritoneal cavity and the abdominal wall was closed in layers with silk. No drains were inserted and no dressings were applied. Immediately postoperatively 50 cc of castor oil was given by means of a stomach tube. No intravenous fluid was given and no effort was made to withhold food or water from the animal.

This chart represents the clinical course in the control animal. The temperature rapidly rose to more than 105 and was stabilized around 104. There was not a great deal of leukocytosis. Death occurred on the eighth day. Autopsy was performed and cultures were taken which were positive for *E. Coli* and *B. Proteus*. There were many loculated, localized abscesses throughout the peritoneal cavity.

This chart represents an animal treated with streptomycin. Twenty-four hours after operation he was given 300 mg of streptomycin daily in divided doses. A leukocytosis occurred up until about the fourth day, which subsided by the seventh day. Treatment was ended on the eighth day. The animal was observed for another week and sacrificed on the 14th day. At autopsy this animal also had a generalized peritonitis with many loculated abscesses.

This chart represents an animal treated with aureomycin. Treatment was started within 24 hours. You will note the marked leukocytosis in the first 48 hours, that dropped rapidly in the next few days. Treatment was ended on the eighth day. The animal was observed for another week and sacrificed on the 14th day. At autopsy the animal was found to have generalized peritonitis. Positive cultures were for *E. coli* and *B. Proteus*. There was very little tendency to localization in this animal, however, he appeared very healthy and alert.

This is the record of one animal we treated with chloromycetin. Treatment was started 24 hours after operation, there was elevation of the leukocyte count with return to normal at the end of about six days. Treatment was ended on the eighth day and the animal was sacrificed on the 14th day. He also had generalized peritonitis.

This is a comparison of the survival rate in the animals that were treated. Only six of the ten controls survived the first four days, only two survived the entire two-week period. Sixty per cent of those treated with streptomycin lived two weeks and nine (90 per cent) of those treated with aureomycin survived for two weeks. The one treated with chloromycetin survived the 14-day period.

DR CHARLES R EDWARDS, Baltimore When surgeons hunt for a new product with which to treat peritonitis it is a healthy sign. Through the years we have seen decreasing mortality from generalized peritonitis, but the mortality rate has not yet reached the point we desire. There is no doubt that a great many patients who have generalized peritonitis and now survive would have died a few years ago. But their survival cannot be credited to the use of the sulfa compounds and antibiotics alone. Good surgery, preoperative hydration and proper postoperative treatment contribute far more, in my opinion, than the antibiotics and sulfa compounds alone would contribute. I am not willing to agree with some men that you can safely close a peritoneal cavity where there is a general infection, and not employ drainage.

The morbidity of patients who have general peritonitis and who receive the gunshot preparations now available is probably greater than ever before, because in many cases of peritonitis that develop very obscure, hidden areas of infection or inflammation, or

both, recovery is prolonged. We still have a lot of gunshot wounds in civilians. Recently a 14-year-old boy went hunting and was climbing over a fence, holding the gun the wrong way, and the gun discharged and blew away most of his abdominal wall, also part of the stomach, all the transverse colon, part of the jejunum and part of the left ureter. The resident operated on him and restored most of these structures except that he had to use the two ends of the colon and bring them out as a double-barreled colostomy. With plenty of supportive treatment the boy survived the primary shock, only to run fever for a long time, and as the course progressed he began to flex his left thigh more and more and complained of pain in the region of the left hip. The operator removed a wad of felt from the shell from the left lateral gutter and the left iliac fossa. Intravenous pyelograms showed function of the left ureter to be satisfactory. Physical examination did not reveal a psoas abscess as would be anticipated because of the complaints, but later an extraperitoneal exploration revealed pulpy degeneration of the psoas muscle, which was responsible for all the symptoms. This had gone on for about five weeks.

Another case to illustrate this was in a man aged about 30, who was admitted 24 hours after a diverticulitis of the sigmoid colon had perforated, he had general peritonitis. He was operated on and drained and a colostomy was done, and he weathered the storm primarily only to run fever for a long time. He complained of soreness in the region of the right diaphragm, but it defied all attempts either by physical or x-ray examination to locate a subdiaphragmatic abscess, as was fully anticipated. After about six weeks of treatment he was permitted to go home and the day before I came down here he was readmitted. Tenting of the diaphragm was very definite, so he had harbored this inflammatory exudate, possibly infection, for about eight weeks. During the year we have had eight cases of generalized peritonitis that have behaved in this manner and, in my opinion, this indicates clearly that the sulfa compounds and the antibiotics that are now available are not sufficient to cure infection. They help to control it, but they do not eliminate it, and these cases will get into trouble later.

I think there is a possibility in these new compounds which will merit investigation and the work will have to be proved clinically later.

THE EFFECTS OF INTRAMUSCULAR AND INTRATHECAL ADMINISTRATION OF STREPTOMYCIN IN NORMAL DOGS AND IN DOGS WITH MENINGITIS DUE TO *ESCHERICHIA COLI**†

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MENINGITIS DUE TO *Escherichia coli* is extremely rare in the adult under peacetime conditions (Rauch and Krinsky,¹ Thompson and Quinn²), although infection of the central nervous system by this organism occurs not infrequently in patients with penetrating wounds (Cairns,³ Ecker⁴) On the other hand this type of meningitis is frequently encountered in infants (Barrett, Rammekamp and Worcester⁵) Indeed, Rauch and Krinsky,¹ after an extensive review of the literature, state that it is the most common type of meningitis in infants under three months of age Before the use of chemotherapeutic agents which have been developed in recent years, the mortality rate of this disease was 80 per cent ⁵

The use of sulfonamides led to a number of reports of recovery in isolated cases,^{2, 6, 7} but the development of streptomycin by Waksman and his associates⁸ offers hope of an even more effective therapy of this and related forms of meningitis Many of the gram-negative pathogenic organisms are highly susceptible to the antibiotic effects of streptomycin and most strains of *E coli* are especially sensitive to the drug (Buggs, Bronstein, Hirshfeld and Pilling⁹)

It is well known, however, that in normal individuals intramuscular administration of streptomycin results in the appearance of only minute quantities in the cerebrospinal fluid (Anderson and Jewell,¹⁰ Heilman, Heilman, Hinshaw Nichols and Herrell,¹¹ Zintel, Flippin, Nichols, Wiley and Rhoads¹²) Although in the presence of meningitis, somewhat larger quantities of streptomycin reach the spinal fluid,^{12, 13} it would naturally be anticipated that intrathecal administration of the drug would offer maximum effectiveness in the treatment of meningitis

Anderson and Jewell¹⁰ and Heilman *et al*¹¹ observed no apparent irritative effects of intrathecal injection of streptomycin Cairns, Duthrie, and Smith¹⁴ reported a moderate pleocytosis after such injections in two patients with brain tumors In one case of tuberculous meningitis and one case of meningitis due to *Ps pyocyanea* (both extremely ill), the same authors reported "fatal reactions" immediately following lumbar subarachnoid injections of 100,000 units of streptomycin and they warned that "in acutely ill patients such injections are not free from danger!" Walker and Johnson¹⁵ reported severe ataxia in

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† This study was aided by the Jack Fies Fund for Research in Neurosurgery and the John B Howe Fund for Research in Neurosurgery The streptomycin was furnished by Merck and Company at the request of Dr Chester Keefer

for the effects upon temperature, pulse rate, respirations, clinical condition, and the cell count and streptomycin level in the cerebrospinal fluid

In 100 animals *E coli* meningitis was produced by injection into the cisterna magna of a suitable number of organisms suspended in 0.5 cc of saline solution. Experiments were done in groups of ten. Five dogs of each group were treated, five untreated.

In a series of 40 dogs, treatment (in half the animals) consisted of daily intracisternal injection of 5,000 units of streptomycin, the first injection 30 minutes after the organisms were injected. Similarly, the treated animals in another group of 30 dogs received only intramuscular injections of 25,000 units

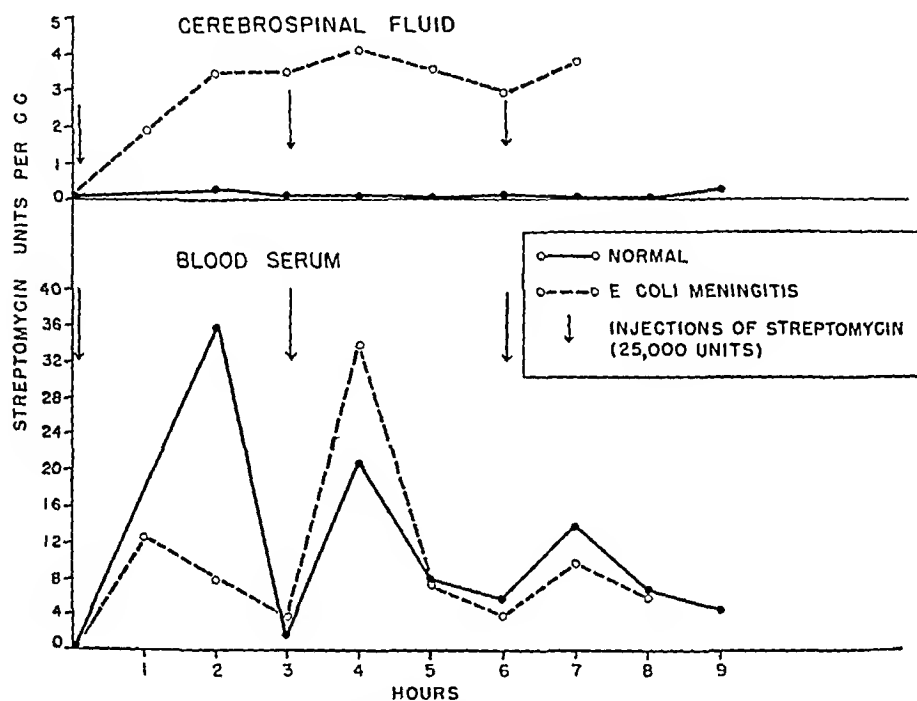


FIG 2—Blood and cerebrospinal fluid concentrations of streptomycin after intramuscular injection

of streptomycin every eight hours, beginning immediately after the injection of organisms. In a third series of 30 dogs, the effects of combined intrathecal and intramuscular therapy were determined in the same way. Treatment was continued for seven days in all animals which survived that long.

Daily blood and spinal fluid cultures were made in all animals.

RESULTS

In normal dogs, intramuscular injection of streptomycin resulted in the appearance only of barely perceptible quantities in the cerebrospinal fluid. In dogs with *E coli* meningitis, the spinal fluid concentration was distinctly higher, but a level of five units per cubic centimeter was the highest obtained. Typical examples of the two groups are shown in Figure 2.

EFFECTS OF STREPTOMYCIN IN DOGS

Intrathecal injection of 50,000 units of streptomycin in a normal dog resulted in immediate stupor, profuse salivation, facial twitching and vomiting, followed by nystagmus and marked ataxia. Four hours after injection, the rectal temperature reached 106° F, respirations were 62 and shallow, pulse rate was 156. The spinal fluid white blood cell count reached 2190 at the same time and was 2700 24 hours later. Abnormal symptoms gradually disappeared within 48 hours.

TABLE I—*The Spinal Fluid Cell Count and Drug Level After a Single Intrathecal Injection of Streptomycin*

Dog No	Dosage Units	Time After Injection											
		1 Hour		2 Hours		4 Hours		6 Hours		24 Hours		48 Hours	
		Cell Count	Drug Level Units per cc	Cell Count	Drug Level Units per cc	Cell Count	Drug Level Units per cc	Cell Count	Drug Level Units per cc	Cell Count	Drug Level Units per cc	Cell Count	Drug Level Units per cc
SCS 1	50 000	210	1990	257	890	2190	262	1680	32	2700	23	675	9
SCS 2	25 000	30	1175	275	540	190	330	1000	150	220	19	75	9
SCS 3	15 000	72	588	220	376	7020	87	5100	32	272	11	110	4
SCS 4	10 000	32	640	100	440	*	80	*	14	1055	**	120	4
SCS 5	7,500	13	536	13	240	90	120	710	90	230	10	80	3
SCS 6	5 000	7	320	25	160	52	140	2250	67	182	9	52	3

* Blood in specimen
** Unsatisfactory assay

Following intrathecal doses of 25,000 units, 15,000 units, 10,000 units and 7500, the same symptoms and signs appeared with progressively diminishing severity and duration. With 5,000 units (roughly 500 units per Kg) moderate lethargy and ataxia were the only symptoms and lasted only a few hours. A marked pleocytosis in the spinal fluid was found with all doses (Table I).

TABLE II—*Survival Time, All Experiments*

	Treated	Untreated
Recovery	35	16
Less than 24 hours	11	17
24-48 hours	0	3
48-72 hours	0	4
3-7 days	3	5
Death after 7 days	1	5

All of these animals retained an effective level of the drug in the spinal fluid for 24 hours or longer (Table I). For this reason, 5,000 units was assumed to be the optimum daily dosage for dogs of this size.

The survival time in all animals with meningitis due to *E. coli* is shown in Figure 3 and Table II. Thirty-five (70 per cent) of the 50 dogs treated with streptomycin recovered as compared with 16 (32 per cent) of the 50 untreated dogs. Of the 15 treated dogs which failed to survive, eleven died within 24

hours, as did 17 untreated dogs. Excluding those animals who failed to live 24 hours the recovery rate in the treated group was 89.7 per cent as compared with 48.5 per cent of the untreated group.

Differences in mortality rates in the three series of control animals are no doubt the result of use of three different preparations of the organisms. However, this does not affect comparative results in each series, since the same preparations were used in both treated and untreated animals of each group.

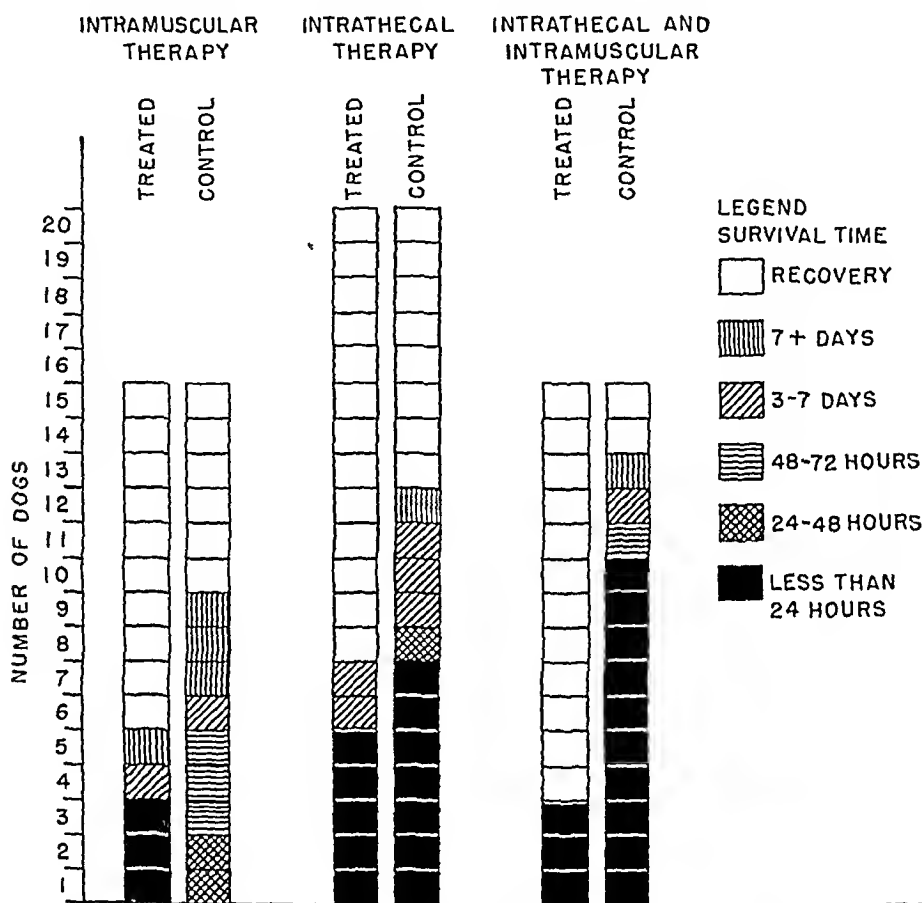


FIG 3—Survival time in meningitis due to *E. coli* in dogs, effects of streptomycin therapy

Independent of this factor, there was a marked difference in the results in the three types of experiment (Fig 3). Intramuscular therapy was limited in effectiveness. The recovery rate was greater in the treated group but the survival time in fatal experiments was greater in the untreated group.

The results of intrathecal therapy alone were more favorable as to both mortality and morbidity, but the differences were not great.

However, the combination of intrathecal and intramuscular therapy resulted in a highly favorable therapeutic effect in the treated animals (Fig 3). Only two of 15 control dogs survived as compared with 12 of the 15 treated dogs. Evidently the preparation of *E. coli* used in this series was particularly virulent,

since 10 of the 15 untreated dogs died within 24 hours. This gives added significance to the high recovery rate in the treated animals.

Figures regarding duration of positive cultures of *E. coli* in blood and cerebrospinal fluid are difficult to analyze, since early fatality means short duration of positive cultures and higher mortality rate means fewer total days in which positive cultures could have been obtained. Despite this "weighting" of the statistics in favor of the untreated series, Table III shows an overwhelmingly unfavorable incidence of positive cultures in the untreated animals.

SUMMARY AND CONCLUSIONS

The effects of streptomycin have been observed in normal dogs and in dogs with meningitis due to *Escherichia coli*. Our observations seem to justify the following conclusions regarding the effects of this therapeutic agent in the dog:

TABLE III—*The Duration of Positive Cultures in Blood and Cerebrospinal Fluid After the First 24 Hours*

Type of Therapy	Number of Days of Positive Cultures					
	Treated			Control		
	No. of Dogs	Blood	CSF	No. of Dogs*	Blood	CSF
Intramuscular	13	8	70	15	19	105
Intrathecal	15	1	25	14	10	102
Intrathecal and intramuscular	12	0	5	5	3	15
Totals	40	9	100	34	32	222

* Eliminating animals failing to survive 24 hours (see text)

1. In the normal dog, intramuscular injection of streptomycin does not result in the appearance of a significant amount of the drug in the cerebrospinal fluid.

2. In dogs with *E. coli* meningitis, intramuscular injection of streptomycin produces a slightly higher, but therapeutically inadequate level in the cerebrospinal fluid.

3. Intrathecal injection of large amounts of streptomycin may produce very marked irritative and toxic effects. The severity and duration of these effects is approximately proportional to the size of the dose.

4. The optimum daily intrathecal dose in the dog seems to be approximately 500 units of streptomycin per kilogram of body weight. This dose maintains an average 24-hour level of the drug in the cerebrospinal fluid approximately as high as do larger doses.

5. Intramuscular streptomycin in therapy of *E. coli* meningitis is ineffective.

6. Intrathecal streptomycin therapy of *E. coli* meningitis is helpful but inadequate.

7. Combined intrathecal and intramuscular therapy of *E. coli* meningitis

has a markedly beneficial effect upon mortality rate, survival time and duration of positive cultures in blood and cerebrospinal fluid

Addendum Since this work was completed, a paper by Lewin (Lewin, W Brit J Surg, 35 266, 1948) has reported eight cases of meningitis due to "coliform organisms" resulting from contamination of wounds None of these was treated with streptomycin

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DISCUSSION —DR WINCHELL MCK CRAIG, Rochester, Minn The progress of medicine has been punctuated by new discoveries which have been used and tested for a final evaluation of their true worth With the advent of the sulfa drugs and the other antibiotics much clinical and laboratory research has been necessary to determine the limitations of these drugs

Foremost among those clinicians who have been conservative in the clinical uses of the antibiotics has been Dr Cobb Pilcher Again he has gone into the laboratory for the purpose of assessing the value of intrathecal and intramuscular administration of streptomycin in treatment of certain infections of the central nervous system While *Escherichia coli* meningitis may be rare, the utilization of streptomycin in the combined method of administration follows the clinical application of the use of penicillin in treatment of other infections

My colleague, Dr Wallace E Herrell who, as you know, has done a great deal of work with penicillin, tyrothricin and streptomycin, has commented upon the use of penicillin as follows "Penicillin has proved exceedingly effective in the treatment of certain infections involving the central nervous system, including meningitis, wounds of the brain and brain abscesses In the treatment of meningitis, penicillin should be administered by the intramuscular route and supplemented by 10,000 units of penicillin dissolved in 5 or 10 cc of physiologic saline solution injected intrathecally every 24 or 48 hours for at least the first few days of the disease"

According to Herrell, many adverse comments upon the intrathecal use of penicillin and streptomycin are based upon the unfair evaluation following the use of too large amounts of the drug Many authors who question the use of intrathecal administration do so because of the pleocytosis which sometimes occurs following its administration, and Pilcher's contribution to our knowledge of streptomycin helps clarify this point Cultures of the spinal fluid should be made after 24 hours and at frequent intervals until a negative culture is obtained

Pilcher has called attention to the fact that the concentration in the cerebrospinal fluid following intramuscular administration of streptomycin is greater than normal in infections of the central nervous system, because more of the drug can pass the blood brain barrier And the therapeutic effectiveness of the drug administered intramuscularly is more effective when augmented by the additional intrathecal administration

According to Herrell, intrathecal administration of this drug is indicated when high concentrations of streptomycin are desired in the cerebrospinal fluid Single injections of as much as 100,000 units (100 mg) in 5 or 10 cc of isotonic solution of sodium chloride have been given intrathecally without evidence of serious reactions, and this amount may be given every 24 hours Before the intrathecal injection is made, a sufficient amount of spinal fluid may be withdrawn to permit bacteriologic and other laboratory studies, including the determination of the level of streptomycin in the cerebrospinal fluid

Streptomycin behaves not unlike penicillin when injected into the body It diffuses rather readily throughout most body tissues and is excreted in certain body fluids such as urine, bile and milk It differs from penicillin in the fact that even large amounts when given by mouth do not penetrate into the blood stream, making it an additional weapon in the preparation of patients for operation on the bowel This is because streptomycin markedly inhibits the growth of the coliform organisms present in the fecal stream Streptomycin is primarily effective against certain gram-negative microbes, whereas penicillin is effective against gram-positive pathogens

Bacteriemia and infections of the urinary tract due to *Escherichia coli* have responded satisfactorily to streptomycin There have been some failures in this group due to the fact that the organism was resistant or became resistant to streptomycin Different types of meningitis have responded satisfactorily to treatment with streptomycin These include infections due to *Hemophilus influenzae* and, in our series, we have one case of meningitis due to *Escherichia coli* which received streptomycin by both the intramuscular and intrathecal routes with a complete cure

The toxic effects of streptomycin are somewhat similar to those of penicillin and respond in the same way following administration of one of the antihistamine drugs such as benadryl or pyribenzamine in doses of 50 mg three times a day. In addition to the cutaneous toxic manifestations such as urticaria or irritative dermatitis, the toxic effects of streptomycin have been nausea, malaise, fever, renal irritation and arthralgia. These forms of toxicity are probably due to impurities. The dermatologic manifestations and involvement of the eighth cranial nerve were the ones most common. The latter results in tinnitus and dizziness and usually follows a long-continued administration of the drug.

Streptomycin can be given intramuscularly and intrathecally in combination with penicillin administered in the same way. In cases in which there is some question with regard to the effectiveness of a single drug, it has been demonstrated that sulfonamides and antiseptics can also be employed safely.

As Doctor Pilcher has pointed out, meningitis from *Escherichia coli* is rare unassociated with penetrating wounds of the brain but, when meningitis does occur, caused either by *Escherichia coli* or other gram-negative bacilli, it is extremely gratifying to know that such studies as he has carried out make the intramuscular and intrathecal administration of streptomycin a safe procedure*.

DR LOYAL DAVIS, Chicago. Doctor Pilcher and his associates have made another contribution to our knowledge concerning the methods, dangers and benefits of the use of the antibiotics in infections of the nervous system and its meninges. Their investigations upon penicillin and the sulfonamides were of basic importance, and to these they have now added important experimental data concerning streptomycin.

To avoid obtaining the wrong impression, it must be emphasized that in doses proper for his experimental animals, the benefits obtained from the intrathecal administration of streptomycin far outweigh its irritative effects. As a matter of fact, Ivy has shown that even the normal spinal fluid of a dog injected intracisternally, or intrathecally, into another dog, also produces irritative symptoms.

The circumstances are similar to those reported upon the effects of penicillin. When this drug was introduced into the ventricles and subarachnoid spaces of experimental animals, symptoms of marked irritation were produced. Yet we, with many others, have used penicillin in 100,000 unit dosages intraventricularly in children with meningitis without residual damage. We have also successfully followed the advice of Wycke of Australia, in using heparin to prevent the formation of a thick fibrinous exudate which often obstructs the cerebrospinal fluid pathways.

Doctor Pilcher points out again that streptomycin, to have its maximum effect, must be used intramuscularly and intrathecally, as is true of penicillin. Again, the effect of infection upon lowering the cerebrospinal fluid-blood barrier is demonstrated in their experiments.

Finally, I would ask only one suggestive question about these most excellent basic experiments. Would histologic study of the meninges and nerve tissue give any more assurance than is offered by evaluation of the clinical symptoms, that in proper dosage no permanent damage will result from the use of streptomycin in cases which are the clinical counterpart of Doctor Pilcher's experiments?

DR COBB PILCHER, Nashville (closing). I want to thank Doctor Craig and Doctor Davis for their discussion. I do not think I can fully answer Doctor Davis' question regarding the histology and the effect produced by streptomycin in these experiments. I may say that sections of the middle ear, acoustic nerve and brain stem have not shown

* Herrell, Wallace E. Streptomycin. Mississippi Valley Med Jour Oct 1947. Reprinted by special permission from J A M A, 132: 200-205, Sept 28, 1946.

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any significant effects of injury. We know that loss of hearing and loss of vestibular function are common in the use of streptomycin. My own feeling is that it is a dangerous drug, and it was with this in mind, as well as other points, that this study was undertaken. We have shown that large doses produce serious symptoms. We have also shown that small doses are safe in animals. The same general results have been found in clinical use, as well as with penicillin. We know that both drugs have a strong irritative effect in large doses intrathecally. Both drugs are still given in large doses, with complications which are usually attributed to the disease, rather than to the drug.

I think our paper should be taken as a warning against large doses of these drugs.

ULTRAVIOLET RADIATION AS AN ADJUNCT IN THE CONTROL OF POST-OPERATIVE NEUROSURGICAL INFECTION

II CLINICAL EXPERIENCE 1938-1948*†

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DURHAM, N C

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IN 1936, HART described the use of ultraviolet radiation for the reduction of postoperative infection from air-borne bacteria in the operating room¹ In subsequent publications, Hart and his associates have presented in considerable detail the bacteriologic and clinical aspects of this problem in the field of general surgery Only preliminary clinical studies were conducted among neurosurgical cases^{1k} This report will include our total experience with the use of ultraviolet radiation as an adjunct in the control of potential postoperative infection among 3,019 clean neurosurgical cases during the time period between January, 1938, and July, 1948 A preceding publication has described the effect of the exposure of atmospheric air plus ultraviolet radiation upon the brains of experimental animals² No structural alterations were demonstrated in these studies that precluded the use of ultraviolet radiation upon the human brain nor has clinical experience suggested any untoward reaction in the exposed cortex when that structure is protected by the usual neurosurgical methods

Although the complicated problem of postoperative infection has been examined at length by general surgeons, there is by comparison little direct experience recorded in our neurosurgical literature Cairns, almost alone in his study of this field, has demonstrated without much doubt that neurosurgical postoperative infection does exist and represents a formidable obstacle to the attainment of consistently good technical results The material of his first report³ and a second review of later clinical investigations⁴ may be summarized as follows

	Operations	Infections	Deaths
1927-1938	968	?	23
May 1938-November 1944	1169	51 (4.4%)	13
December 1944-March 1947	670	6 (0.9%)	0

After November, 1944, Cairns began the prophylactic local use of a mixture of penicillin and sulphamezathine with an attendant marked reduction in

* See "The Effects of Ultraviolet Radiation on the Exposed Brain Experimental Study," by Guy L Odom, Henry M Dratz and F V Kristoff, to be published in the July ANNALS OF SURGERY

† Read before the Southern Surgical Association, White Sulphur Springs, W V, December 8, 1948

infection rate. He states that the six infections recognized during this period were severe and might have been fatal without vigorous antibiotic therapy.

A subsidiary but important by-product of this effort in the reduction of postoperative infection was the finding that the brain may be susceptible to infection by organisms normally regarded as saprophytes or contaminants.⁵

A second as yet unpublished summary of the incidence of postoperative neurosurgical infection has been made available to us through the generous co-operation of Dr. Wilder Penfield, Director of the Montreal Neurological Institute.⁶ Every possible effort has been made in that clinic to control the many factors perhaps responsible for postoperative infection. Doctor Penfield's results are particularly significant since they illustrate a reduction in infection rate through the adjuvant use of a modified form of ultraviolet radiation. A definition of the character of these infections is not available. The yearly infection rates are given by Doctor Penfield as follows:

Year	Cases	Number of Infections
1912-13	695	4
1913-14	760	10
1914-15	858	11
1915-16*	968	4
1916-17	871	2
1917-18	914	4

* Installation of modified form of ultraviolet radiation

The recognition by Cairns and Penfield of the existence and danger of postoperative infection among neurosurgical cases has in each instance resulted in the steady reduction of the infection rate, by different methods, to a relatively negligible factor. If further evidence is required to substantiate the fact that the problem of neurosurgical infection is a real one, and often unanswered, it may be obtained by reading the neurosurgical literature of the time period covered by our report. In four American surgical and neurosurgical journals in the time period January 1, 1938, through January 1, 1948, 2,710 clean neurosurgical cases are reported, among whom 20 patients died as a sequel of postoperative infection.

The statistical data of our survey, with a brief discussion of the findings are as follows:

TABLE I—General Summary

Total clean operative procedures	3 019
Total infections	42
Severe 12 4%	
Mild 25	
Stitch abscess 5	
Deaths attributable to infection	1
Infection percentage rate	1.39

TABLE II—*Infections per Year*

	Number of Procedures	Infections	Deaths
1938	170	0	0
1939	202	2	0
1940	275	3	0
1941	190	4	1
1942	232	0	0
1943	210	2	0
1944	252	4	0
1945	321	5	0
1946	425	11	0
1947	477	9	0
1948 (6 months)	265	2	0
Totals	3 019	42	1

TABLE III—*Infections in Specific Operative Procedures*

	Number of Cases	Number of Infections	Deaths
Craniotomy	1,228	13	1 05%
Removal of ruptured disk	1 063	19	1 77%
Laminectomy	271	6	2 21%
Other*	457	4	90%

* Includes procedures such as lobotomy, trephine removal of extradural or subdural hematomas resection of meningoceles peripheral nerve operations sympathectomies scalenotomies ligation of internal carotid artery in the neck and the like

TABLE IV—*Predominating or Single Infecting Organism*

Hemolytic <i>Staphylococcus aureus</i>	14
Nonhemolytic <i>Staphylococcus aureus</i>	10
Nonhemolytic <i>Staphylococcus albus</i>	5
Culture negative	13

DISCUSSION

The duration of hospitalization or the duration of secondary wound healing the intensity and length of elevated temperature rates, the threat to life or bodily function and the necessity for intensive antibiotic therapy were factors by which the severity of any one infection in this series was measured Twelve infections were considered to be severe, 25 mild and five were noted as simple stitch abscesses The incidence of infection was higher in lumbar laminectomies than in craniotomies or upper spine laminectomies The rate of the severe infections was approximately 4 per cent

In seeking a cause for individual infection, other than the acknowledged one of air contamination, it is interesting that 27 of the infections were related, if not directly attributable to defects in neurosurgical technique or errors in neurosurgical management Thus, 12 infections followed the early appearance of operative hematomas, either with or without wound disruption,

five were subsequent to scalp flap necrosis, two appeared when craniotomies were drained through an adjacent stab-wound, two were related to the retention of foreign bodies (triangular fluffs), two occurred in disc procedures in patients who harbored a single cutaneous furuncle, one in a patient with a mild generalized dermatitis, one followed repeated ventricular taps, one occurred in a craniotomy wound that had been packed to control hemorrhage, and one was noted ten days after a tantalum cranioplasty of exceptional magnitude. If these infections were related to extraneous factors, the number presumably due to contamination by air-borne bacteria is significantly reduced.

Among the infections in which a positive culture was obtained, the organism represented some type of staphylococcus, a finding that has been previously demonstrated by Doctor Hart. No seasonal variation was noted in the relatively few infections. The average hospital stay for the patients with any form of infection, severe or mild, was 29.4 days as compared to the average stay for all patients in the year 1947 of 12.7 days. These patients were operated upon by two staff neurosurgeons and the resident neurosurgeons present during the ten-year period of the study.

Summary of case fatality attributed to infection

Duke Hospital History A-52261, colored male, age 17, was admitted in a stuporous condition to the Neurological Division of the Medical Service on December 3, 1940. Generalized headache had developed 4 weeks prior to admission and the patient had become comatose 4 days before admission. Neurological examination showed, in brief, bilateral papilledema, right hemiparesis and hyperreflexia of the right-sided muscle-tendon reflexes. A provisional diagnosis of tuberculous meningitis was entertained and lumbar puncture demonstrated 100 mononuclear cells, a positive Pandy reaction and increased subarachnoid pressure. All other studies were essentially normal. A left frontal craniotomy was subsequently performed (B. W.) and the left frontal lobe was resected. The resection plane passed through a necrotic neoplasm situated in the base and lateral border of the anterior horn of the ventricle and extending caudally in the temporal lobe. On the seventh postoperative day, in spite of repeated ventricular drainage to reduce pressure, the medial limb of the craniotomy incision ruptured. Later culture from the persistent cerebrospinal fistula showed the presence of non-hemolytic staphylococcus aureus. Death occurred 22 days after operation and autopsy revealed a purulent leptomeningitis. The tumor, disclosed at operation, invaded the left fronto-temporal region, crossed through the corpus callosum and infiltrated the right frontal lobe. The pathologic diagnosis was glioblastoma multiforme.

SUMMARY

Ultraviolet radiation has been used as an adjunct in the prevention of neurosurgical infection during the time period between January, 1938, and July, 1948. Clinical experience with 3,019 clean neurosurgical cases has demonstrated subsequent wound infection in 42 of these cases, an incidence of 1.39 per cent. Twelve of these infections were severe, 25 were considered mild.

and five were recorded as simple stitch abscesses. *Staphylococcus aureus* and *albus* were the predominating infecting organisms. A considerable number of wound infections appeared to be related, not only to the factor of bacterial contamination from the air, but also to errors in neurosurgical technique and management. In our opinion, this clinical study over a ten-year period indicates that ultraviolet radiation should be considered an important adjunct of the neurosurgeon's armamentarium.

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DISCUSSION —DR DERYL HART, Durham, N. C. I believe Doctor Woodhall has leaned backward in including every possible infection in his cases, and in ascribing the one death to an operating room infection, that is, an infection originating during the operation. This man disrupted his wound ten days after operation and died 22 days following operation, at which time there was infection in the wound after it had been draining for 12 days.

In the publications I have made on unexplained infections in operative wounds, we eliminated all the cases where there was an evident cause of infection, such as operation

on a perforated appendix, prolonged drainage of a wound, such as Doctor Woodhall reports, *etc*

Before we introduced ultraviolet radiation in the operating room we had a number of severe, unexplained infections. Infections occur in cycles associated with bacterial spread over the country. Everyone is familiar with the spread of streptococcal organisms following the 1918 epidemic of influenza and the prevalence of streptococcal wound infections which followed. In the course of six years, during which we had 15,000 operations in a new hospital, we had 17 unexplained deaths in clean wounds. These were serious infections with meningitis, septicemia, and peritonitis predominating, all were fairly large operative procedures, mostly thoracoplasties, orthopedic operations or cranial operations. We did not have fatal infections in the general run of operative procedures, but occasional infections did occur.

The organisms in fatal and non-fatal infections were predominately *Staphylococci*. As illustrating the cyclic curve of infections, I would like to call attention to the fact that in one three-month period we had 35 per cent of all deaths from "unexplained" infections in this five-year period while we were doing approximately 15 per cent of the total number of operations. At this time in December, January and February, there was an epidemic of *Staphylococcus aureus* contamination of the nose and throat in the people of the community, 75 per cent of the people in the operating room personnel and in the general population had this organism in their noses and throats. During such time infections are almost inevitable if many large surgical operations are performed without some provision for preventing organisms from entering the air or for killing them in the air. The number of organisms in the air of the operating room diminishes greatly during the summer. When the organisms are in the noses and throats in great number, they are also in the air.

Doctor Woodhall and other members of the staff started using ultraviolet radiation at their own request, and it is now used routinely for most large clean operations. Between 50,000 and 100,000 operations have been performed in the Duke Hospital during the past 10 years. About 10 per cent of these have been large, clean procedures protected with ultraviolet radiation.

I have not made a complete survey recently, but have followed the matter of infections closely and I do not believe that there has been any death resulting from an unexplained infection during this period, unless this one reported by Doctor Woodhall is considered as unexplained.

REDUPLICATION OF THE STOMACH*

REPORT OF A CASE

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REPRODUCTIONS of the gastro-intestinal tract are a relatively uncommon occurrence. The term "enterogenous cyst" has been applied to these reduplications, which may occur in any part of the gastro-intestinal tract from the esophagus to the sigmoid. They are most commonly seen in the ileocecal region and decrease in frequency generally proximal to this point. About 15 cases have been reported in the literature as occurring in the duodenum, and the case reported herewith is the third recorded instance of reduplication of the stomach.

Enterogenous cysts are closely related embryologically to congenital diverticula. Meckel's diverticulum occurring as a failure of closure of the omphalo-mesenteric duct is the commonest form of congenital diverticulum. Cysts occurring in this region usually represent remnants of this embryological structure. These cysts, wherever they occur in the intestinal wall, may be intermuscular, submucosal or subserosal, or may occur as a reduplication anatomically similar to the normal gastro-intestinal tract which they duplicate, as in the case of reduplication of the stomach reported by Ladd and Gross. In isolated instances, cysts have lost their connection with the wall of the intestine and may occupy a position between layers of the mesentery somewhat removed from the parent gut. The uniform characteristic of these cysts is that the structure of the cyst wall resembles the intestinal wall from which it was derived. Occasionally, intra-cystic pressure or inflammatory changes may produce variations in the epithelial lining of these cysts.

Symptoms produced by these cysts in the intestinal tract vary with their location and are usually manifested by evidence of obstruction, infection, or both, and rarely by the presence of a palpable mass. Most often symptoms are produced which lead to recognition of these cysts at laparotomy in early infancy, but our case of reduplication of the stomach was 27 years of age. The pre-operative diagnosis of such a cyst is extremely unlikely, although a presumptive diagnosis may be made rarely in the presence of a palpable mass with obstructive symptoms.

Treatment of enterogenous cysts has varied widely with different observers and it may be said that each cyst presents a problem which must be solved individually. Removal of a cyst without entering the bowel lumen is frequently impossible because it is so intimately attached to the wall of the bowel. Resection of the bowel and its contained cyst is usually the method of choice. In cysts of the duodenum, resection or total removal may be impossible because of the danger of damage to the common or pancreatic ducts. Attempts to drain these

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cysts externally have usually resulted in failure because of their tendency to recur. External drainage of such cysts was attempted in both of the cases of enterogenous cysts of the stomach previously reported and apparently was successful in the case of Ladd and Gross. The method of internal drainage suggested by Gardner may be the method of choice in some instances.

The case reported by Ladd and Gross was that of a seven-year-old girl whose reduplication of the stomach closely simulated the adjacent normal stomach. Symptoms which led to a laparotomy were a vague gastro-intestinal disturbance and roentgen-ray evidence of encroachment on the normal stomach



FIG 1—Roentgenogram of stomach demonstrates prominence of mucosal pattern with evidence of extrinsic pressure on duodenal cap

lumen along the greater curvature. Treatment consisted of marsupialization of the mass with subsequent débridement and packing with gauze. The case of Ferraro occurred in a six-months old child. Symptoms consisted of the presence of a mass in the left upper quadrant which was incised when the child was six weeks old. The operative area continued to drain a watery fluid until laparotomy was performed at the age of six months. At operation the cyst was removed from the stomach along with a small portion of the stomach wall

The wound healed well, and recovery from the cyst was apparently satisfactory. The child died later of worm infestation and malaria.

CASE REPORT

F I F (No 24675—Columbia Hospital), age 27, was admitted to the Columbia Hospital October 9, 1947. He stated that he had been suffering abdominal discomfort for six months prior to admission. Pain was not severe but consisted of a tugging sensation just to the right of the umbilicus (at the top of an old right rectus incision for appendectomy). This tugging sensation had been present in some degree since appendectomy in 1942 but was more severe lately. His discomfort was aggravated by activity. A feeling of fullness in the stomach and slight nausea after eating were prominent, but other digestive disturbances were minimal. At intervals since the onset

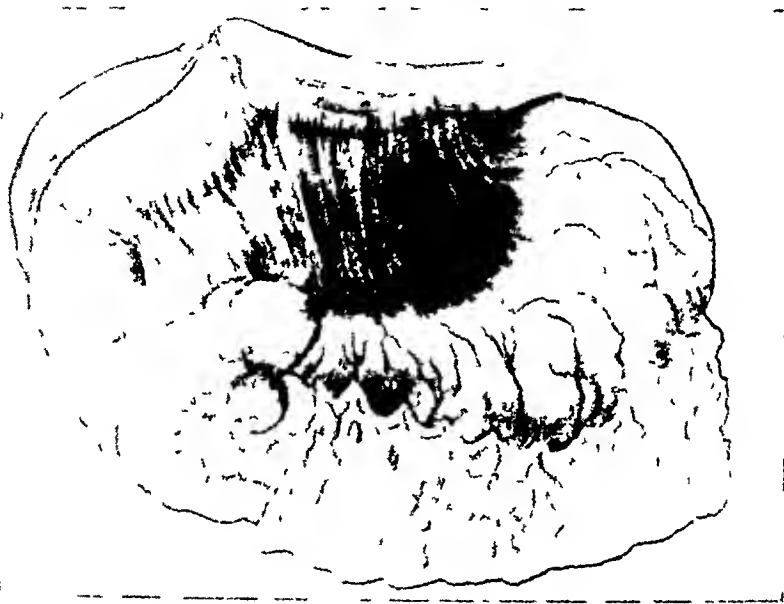


FIG 2—Illustrates position of cyst within stomach wall. Portion of cyst imbedded in stomach wall is identified by dotted outline.

of symptoms he had run a low-grade fever. All efforts to trace down the cause of this fever were fruitless. He had lost 13 pounds since the onset of symptoms.

Family History Negative.

Past History Tonsillectomy in 1932. Appendectomy in 1942 for acute appendicitis.

Laboratory Examinations Total white and differential counts had been repeatedly normal. Urinalysis was normal. "Fever tests" and smears for plasmodia had been repeatedly negative. Roentgen-ray examination revealed the presence of an obstruction in the region of the duodenum in the opinion of one radiologist. Repeat roentgen-ray examination produced the following report (Fig 1):

"Examination of the stomach, duodenum and esophagus demonstrates a pronounced prominence of the gastric and duodenal mucosal pattern with a slight diminution in peristaltic vigor. No hernia or ulcer can be demonstrated. The duodenal cap is flattened but its contour is not that of ulcerative disease. Opinion: Generalized hypertrophic gastroduodenitis of marked degree. To be considered are the possibilities of lymphoblastoma and allied conditions."

Physical Examination Essentially negative except for slight tenderness just to the right of the umbilicus at the upper end of a lower right rectus incision.

REDUPLICATION OF STOMACH

Operation On October 10, 1947, exploratory laparotomy was performed. The cavity was entered through an upper midline incision. Adhesions to the abdominal wall were absent. Thorough exploration was carried out, and no pathologic condition was detected except at the lower end of the stomach. At this point a cyst was found on the anterior aspect of the stomach near the pylorus (Fig 2). Palpation of the pyloric end of the stomach revealed that the major portion of the cyst was buried deep in the gastric wall or was actually intraluminal. The cyst could not be emptied by gentle compression. Edema of tissues adjacent to the cyst evidenced a low-grade inflammatory process. A window was made into the stomach, and the cyst was found to be beneath the mucosa. The portion of the cyst within the stomach wall was dissected out (Fig 3). This wound was closed with o chromic catgut reinforced with No. 40 cotton. The window into the stomach lumen was closed by the same method.

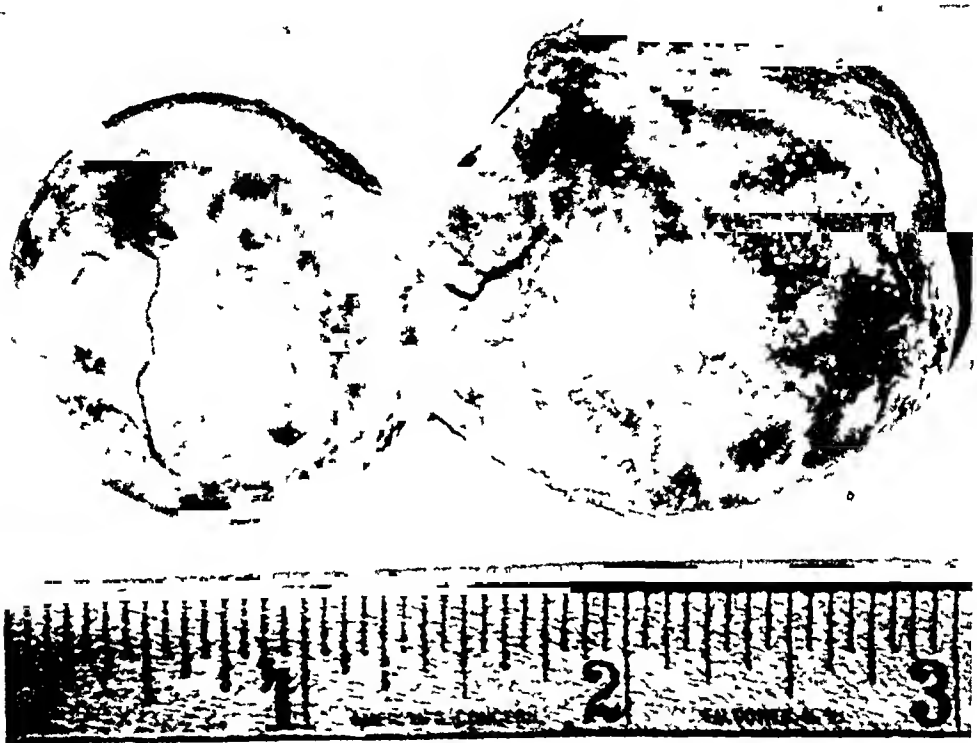


FIG 3—Intact cyst after removal. Four-fifths of larger portion of cyst was imbedded in the stomach wall.

Pathologic Report "Received an hourglass-shaped structure removed from the stomach wall. It consisted of two cysts which connected one with the other. One cyst was 5 cm in length and $3\frac{1}{2}$ cm in diameter. The other cyst was $6\frac{1}{2}$ cm in length and 4 cm in diameter. The two cysts were tense with fluid material which could be pressed from one cyst to the other. On gross sections, the walls appeared to be fibrous tissue in character, and the contents were yellowish in color, very thick and mucinous and sticky in character. The inner walls were finely granular in appearance and yellowish in color.

"Microscopic sections of this tissue show that the walls of the cysts are made up of involuntary muscle fibers and fibrous connective tissue. The cysts are poorly lined by a single layer of small, atrophic, deep-staining epithelial cells. No inflammatory reaction is seen in the tissue. There is no evidence of any malignancy in the sections.

"It appears that this double cyst is an outpouching of a part of the stomach wall which has subsequently lost all direct communication with the stomach cavity.

"Diagnosis Double (hourglass) cyst of the stomach"

Postoperative Course Uneventful except for the development of mild thrombophlebitis on the tenth postoperative day Follow up report of recent date reveals that he is completely relieved of symptoms and considers himself entirely well

DISCUSSION

- 1 The third recorded case of enterogenous cyst of the stomach is reported
- 2 Unique features of this case are
 - a The fact that he was 27 years old before his disease was discovered
 - b Production of low-grade temperature by inflammatory reaction within the cyst
 - c The presence of chronic interference with emptying of the stomach

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DISCUSSION—DR THOMAS D SPARROW, Charlotte N C In more than 9000 pediatric admissions to the Charlotte Memorial Hospital during the past eight years, we have encountered two cases of reduplication of the intestinal tract One of these cases was a girl eight years of age She was admitted to my service and presented such findings that I feel they are worth recording The child was brought to the hospital because one month previously, she had had a frank hemorrhage of bright blood from the bowel which clotted after passing The parents stated that since infancy she had complained of intermittent cramping pains about the umbilicus and on frequent occasions had passed blood in the stools At six months of age she vomited a considerable amount of blood and on one or two occasions, she coughed up bright red blood At that time two bronchoscopic studies were made It was thought that the bleeding was due to tuberculosis of the peribronchial glands, however, tuberculin tests were negative At 13½ months of age she vomited blood and blood was noted in the stools When three years of age her weight

was 27 pounds, although she was anemic and was passing tarry stools. At four years of age, because of the pain in the abdomen, her appendix was removed.

On admission to the hospital she appeared to be a perfectly normal child of eight years of age. Physical examination was entirely normal and x-ray studies of the chest and intestinal tract were normal. She was quite anemic and her stools definitely contained blood. The Department of Pediatrics was unable to find any definite cause for bleeding and a tentative diagnosis of Meckel's diverticulum with ulceration was made. She was prepared for operation by giving her several small transfusions.

At operation the terminal ileum was found to be entirely normal but, on exploration of the intestinal tract, a reduplication of the jejunum was encountered. It began about 10 centimeters along the jejunum. At its distal end, the reduplication or diverticulum communicated with the jejunum. At its proximal end there was a large, bulbous-like structure, buried between the folds of the mesentery. The mesenteric vessels could be seen crossing the reduplication before entering the jejunum. Forty-eight centimeters of the jejunum, including the reduplication, was resected and a side-to-side anastomosis was performed. The child made an uneventful recovery and was allowed to leave the hospital on the eleventh day (slides).

The first slide shows the normal jejunal mucosa. The second slide shows the mucosa of the reduplication which closely resembles that of the stomach. In the bulbous-like structure of the proximal end of the reduplication there was an ulcer, which was the source of the hemorrhage and which closely resembled the ordinary peptic ulcer.

Gross has described the symptoms produced by these lesions under three headings: Obstruction of the alimentary canal by regional external pressure, pain produced by distention of the cystic mass, and hemorrhage caused by interference with the intestinal blood supply, leading to sloughing of the intestinal mucosa. We believe the pain and hemorrhage in the cases seen in our hospital were probably due to ulceration of the gastric-like mucosa. The symptoms may be indistinguishable from those of Meckel's diverticulum with ulceration and hemorrhage. In those cases diagnosed as Meckel's diverticulum in which the lesion is not found, a thorough investigation of the intestinal tract should be made in search for a possible duplication.

THE MANAGEMENT OF PATIENTS WITH BLEEDING FROM THE UPPER GASTRO-INTESTINAL TRACT WITH BUFFER AND THROMBIN SOLUTION*

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IN RECENT YEARS the concept with regard to treatment of bleeding from the upper gastro-intestinal tract has changed. Fortunately, within the past 15 years, progress has been made which has led us away from the old idea of starvation and heavy sedation in these cases. The contributions of Andresen¹ and Muelengracht² were an advance over the watchful-waiting method of dealing with bleeding peptic ulcers in that some nutrition and materials were supplied to counteract the ill effects of the acid of the stomach, but development of operative methods for stopping hemorrhage was not stimulated. Within the past ten years there has been a tendency on the part of surgeons to consider the importance of control of hemorrhage rather than to wait for the hemorrhage to stop because of lessened blood volume and the resulting decrease in blood pressure.

In instances in which the hemorrhage from an ulcer was not great and the patient was in good condition, the Andresen or Muelengracht type of treatment was successful. Once the hemorrhage stopped and an adequate thrombus was formed in the bleeding vessel, repeated small feedings and rest in bed were usually sufficient to decrease the acid and to permit healing to take place. In cases in which the bleeding was vigorous or the patient was unable to withstand the resulting hemorrhage, death occurred. All too often if surgical intervention was resorted to, it was carried out upon patients who had become exsanguinated through continuous bleeding for several days or, what in general appeared to be worse, through repeated severe hemorrhages. The surgical mortality under these conditions could not be expected to be low.³ The experiences undergone during World War II revealed that a patient could stand fairly massive acute hemorrhage if sufficient quantities of blood were replaced immediately. There were those who thought that if a patient was bleeding excessively, the most direct and efficacious method of handling the problem was to ligate the bleeding vessel. This has always been a primary principle in the control of hemorrhage—to ligate the bleeding vessel or stop the hemorrhage by pressure, especially if the bleeding is from a surface wound.

The only difficulty encountered in bleeding from the gastro-intestinal tract is lack of accessibility to the bleeding area. Since principles are very much the same regardless of the site of bleeding, many surgeons believe the best approach to the problem of a patient bleeding from the upper intestinal tract

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is a direct and early one. With adequate blood available for replacement during the operative procedure a sufficient margin of safety is afforded to permit the surgeon not only to stop the bleeding but in many instances to carry out definitive treatment for the peptic ulcer. Two deterrents exist to prevent wide acceptance of the dictum that all bleeding peptic ulcers require immediate surgical intervention. One of these is that in the majority of cases the bleeding stops spontaneously, the other is that it is not always possible to localize the site of the bleeding or to determine accurately its cause or its extent.

From a review of the literature^{4, 5, 6, 7, 8} relating to the treatment of bleeding peptic ulcers, several important points have been stressed. In the older age group the mortality from bleeding from the upper gastro-intestinal tract is more serious than in younger individuals. This is as might be expected. Many have related this increased mortality to specific reasons, such as the changes incident to age in the blood-vessel wall. A much more plausible explanation would take many more of the factors of age into account. Some authors have been inclined to the view that patients over 40 should have operative intervention for bleeding from the upper intestinal tract, while others feel that the lower limit for surgical intervention is the age of 50. It is readily seen from a study of any large series that mortality may result from bleeding peptic ulcer in any age group.

This would lead us to the belief that more important criteria are the ability of the patient to withstand hemorrhage and the amount of hemorrhage that is present. It seems obvious to us that no sharp dividing line can be drawn, and that the patient must be considered individually.

One other fact that seems clear to us is that patients who have repeated massive hemorrhages do poorly as compared with those having a single episode of bleeding. From our own experience we find that long-continued bleeding likewise adds a hazard for the patient. In the case either of long-continued bleeding or repeated hemorrhages, surgical intervention is quite likely to be resorted to, and in these individuals surgery is more hazardous than in those who suffer from a single massive hemorrhage.

Of the cases of upper gastro-intestinal bleeding reported in the literature, duodenal and gastric ulcers are the commonest causes. Bleeding from esophageal varices, gastric malignancy or other causes form only a small percentage of the total number.

It is difficult to obtain reliable information for most of the series reported in regard to the amount of blood lost. Some have attempted to determine this on the basis of hemoglobin determination or red-cell count. In cases in which blood transfusions are not given, the hemoglobin level, especially if known before bleeding occurred, serves as a rough index but is not a reliable means of determining the amount of blood a patient has lost.

About three years ago we were confronted with a serious problem in relation to a patient who had had bleeding almost continuously for four days. He had been supported during this interval by blood transfusions which were

inadequate to maintain his hemoglobin above a level of 6.7 Gm per 100 cc. The patient was not in very good general condition, the problem of anesthesia seemed hazardous, and because of his size and build, operation appeared difficult. Under the conditions presented, operative intervention seemed to us to be an almost hopeless gesture. Since one of our number was working on a fundamental problem relating to thrombin and the bleeding seemed not too vigorous, it appeared worth while to attempt to stop the hemorrhage by the use of topical thrombin^{9, 10, 11}. It was obvious that if the thrombin were to work it would be necessary to neutralize the hydrochloric acid in the stomach, and for this purpose copious amounts of phosphate buffer were used. The bleeding stopped promptly and the patient responded immediately to blood transfusions and made an uneventful recovery.

Since that time we have used thrombin and buffer in over 100 cases of bleeding from the upper gastro-intestinal tract. Variations in the use of this method have been employed. In the first 64 cases the buffer and thrombin were administered by mouth or inserted in the stomach through a Levin tube. In the first group of cases, attempts were made to stop the hemorrhage without other considerations. It soon became obvious to us that the method could be used not only to stop the hemorrhage but also to determine whether or not the hemorrhage was controlled. With the tube in the stomach and with gentle suction applied, it was possible to tell whether bleeding was continuing, for we noted in the cases in which the bleeding had stopped that the material aspirated from the stomach contained very fine, brown granules of clotted blood, whereas in the case of continued bleeding, large, loose clots having a different color and texture were noted, and in some instances fresh blood was removed from the suction tube.

The method which we have found most effective in the management of hemorrhage from the upper gastro-intestinal tract is as follows. A Levin tube is passed through the nose into the patient's stomach. The stomach is then washed with buffer solution or saline, and following this, 50 cc of seventh-molar phosphate buffer* is introduced into the stomach. This is allowed to remain for five minutes. An additional 50 cc of phosphate buffer is introduced, and with it 10,000 units of topical thrombin†. The tube is then clamped for a half hour. During this period blood studies are made, and if the patient appears to be suffering from serious blood loss, a transfusion is given. After 30 minutes the clamp is removed from the Levin tube and slow, gentle suction is applied. For this purpose we have utilized a pump with a valve mechanism which permits of low suction, not to exceed a foot of water. The material removed from the suction tube is observed through the glass connector. If the bleeding has stopped, the material removed usually appears finely granular and

* 20.4 Gm of di-sodium phosphate in a liter of water

1.95 Gm of di-hydrogen potassium phosphate in 100 cc of water

These are then mixed, producing 100 cc of seventh-molar of phosphate buffer, pH of 7.6

† The thrombin for this study was kindly supplied by Parke-Davis & Company

light-colored, if bleeding is continuing, fresh, blood-stained material can be seen in the tube. If there is no further evidence of bleeding from the stomach, 50 cc. of buffer solution is introduced every half-hour, allowed to remain a half-hour and then aspirated. The buffer may be applied by slow drip. This process is carried on for several days. In cases in which bleeding continues, the process is repeated. If, however, the bleeding appears to be uncontrolled by thrombin administration, other measures for controlling hemorrhage are resorted to.

TABLE I—*Cause of Bleeding*

	Con- trolled	Controlled, Recurred		Not Con- trolled	Not Con- trolled	Died from Bleeding
		Then Controlled by Thrombin Operation				
Duodenal ulcer	36		4			
Peptic ulcer—site unknown	15			1		1
Bleeding—site unknown	7			1		1
Gastric ulcer	6	3				
Esophageal varices	7			2	1	3
Malignancy	4					
Miscellaneous	12		1			
	—	—	—	—	—	—
Total	87	3	5	4	1	5

There is a question which cannot always be answered relating to whether the bleeding is coming from an ulcer of the stomach or duodenum, or whether it is due to esophageal varices. More recently, in cases of doubt, we have utilized the technic developed by Patton,¹² which we have found will effectively control bleeding from esophageal varices and at the same time permit us to tell whether the bleeding is from the esophagus or below. In rare instances it has been possible for us to determine that the bleeding was from esophageal varices because the patient vomited blood at the instant that clear material was coming from the stomach through the Levin tube.

We have analyzed the data from the first 100 cases in which thrombin and buffer were used. The data were collected at the time the patient was in the hospital as it was recognized that the use of this material was on an experimental basis. There was no attempt to select cases. All cases in which there was more than minimal bleeding from the upper gastro-intestinal tract were studied. Cases in which there was evidence of peptic ulcer on the basis of history but in which there was no localization of the site of the ulcer either by roentgen-ray or operative findings, were classified as peptic ulcer. Only those cases in which there was proof of the site of the ulcer were classed as duodenal or gastric ulcers. In the case of bleeding from esophageal varices, we required fairly reliable proof before classifying them as such. Such proof consisted of demonstration of the varices by roentgenogram, esophagoscopy, postmortem examination or the presence of cirrhosis of the liver without evidence of the presence of ulcer. Cases in which we could not be reasonably sure of the

source of the bleeding during the patients' stay in the hospital were classified as "site unknown." A miscellaneous group of cases in which the source was reasonably certain were as follows: hemorrhagic gastritis 6, retroperitoneal sarcoma 1, congenital short esophagus 1, hemorrhage from gastric suture line 2, gunshot wound postoperative 1, chemical gastritis 1, pseudodiverticulum of duodenum 1. Table I indicates the distribution of the cases as to diagnosis. Eighty-seven were controlled by the use of thrombin buffer alone. In eight additional cases the hemorrhage was controlled by the use of thrombin buffer but it recurred. In three of these eight cases it was possible adequately to control hemorrhage again by the use of buffer, but in five it was felt that operation was a more effective means of controlling the hemorrhage. There were four cases in which bleeding recurred after having been controlled with thrombin and further treatment was ineffective. These patients were not operated upon, and the hemorrhage was not controlled. One other case died from massive hemorrhage in which the bleeding was at no time controlled.

TABLE II—100 Cases Treated with Thrombin and Buffer

Hemoglobin Levels	Stopped		Stopped Recurred Then Controlled	Stopped Recurred Not Controlled With Thrombin	Not Controlled at All
	1st Rx	Multiple Rx			
0-2	1	1			
2-4			1		
4-6	7	6		2	2
6-8	13	6		2	1
8-10	21	10	1		
10-12	8	1			
12 and above	6	7	1	3	
Total	56	31	3	7	3

An attempt was made to obtain information relative to the amount of bleeding. It was not possible to determine the amount of bleeding by measurement of the vomitus because in many instances blood was lost into the lower gastro-intestinal tract, the vomitus was mixed with food and gastric juice and, in most instances, blood had been lost before the patients were seen by us. It is well known that a study of hemoglobin levels is an unreliable measurement of the amount of blood lost, not only because of the factor of concentration but also because it is quite impossible to determine in these cases what the level of the hemoglobin was before the bleeding started. In addition, it was not always feasible to obtain hemoglobin determinations before transfusion was given since it is customary in our hospital to begin transfusion on exsanguinated patients as soon as they arrive in the emergency ward. The majority of the hemoglobin levels were made in these cases after one or more transfusions had been given. So far as the hemoglobin determinations are concerned, the majority of these patients give no indication of the actual amount of blood lost. The data are presented as the only means at hand other than clinical evaluation for estimating the amount of blood lost. We

recognize that this is a very rough estimate and in most instances, the hemoglobin levels were higher than the clinical appearance of the patient indicated. As can be seen from Table II, the hemoglobin levels gave no indication as to whether or not it would be possible to stop the hemorrhage by one or multiple doses of thrombin or whether the thrombin would be entirely ineffective. One might expect that the greatest number of deaths would occur in those patients who presented the lowest initial hemoglobin levels. Yet two of the patients whose initial hemoglobin levels were too low to be determined survived, while another with a hemoglobin of 13 continued bleeding and died. The hemoglobin levels in the table represent initial determinations. The data do not represent the lowest hemoglobin levels obtained from the patient, nor do they indicate the amount of hemoglobin available to the patient just before death.

Table III illustrates the ages of our cases—for the most part, in terms of decades. While we recognize the fact that the series is small, it is worthy of note that there is approximately the same incidence of deaths from hemorrhage

TABLE III — *Incidence G. I. Tract Hemorrhage—100 Cases*

Age Incidence	5		20		30		40		50		60		70		80		81	
	6		to		to		to		to		to		to		to		to	
	Months		20		30		40		50		60		70		80		1	
	1	0	3	18	31	26	14	6	1									
Death from hemorrhage (5)					2				2		1							
Death from other causes (7)					1	1	3	1	1									
Total deaths (12)					3	1	3	3	2									
86 White																		
14 Negro																		
88 Male																		
12 Female																		

in the 30 to 40 age group as is found in the 60 to 70. There were no deaths from hemorrhage in the age group 40 to 60. We are quite certain that the five cases listed as deaths from hemorrhage occurred from loss of blood. In patients who died from other causes, loss of blood played a minor role, if it contributed at all. One patient died following a gastrectomy performed several weeks after he had recovered from his bleeding episode. The gastrectomy was performed to cure his ulcer, and the patient died in cardiovascular collapse with a hemoglobin of 13 and without evidence of postoperative hemorrhage. One patient died from severe diffuse peritonitis, another from duodenal fistula, and another death was due to severe uremia unassociated with the bleeding period. One patient had severe diabetes mellitus and cirrhosis of the liver, another had widespread metastases of carcinoma in the liver and died from pneumonia, while another died in delirium tremens. In none of these seven cases did any fresh hemorrhage precede death.

Despite the fact that the population of our hospital is predominantly Negro, the majority of patients who suffered from bleeding of the upper gastrointestinal tract were white, there were 86 white people in this series and 14 colored. Eighty-eight of the patients were males, while 12 were females.

DISCUSSION

Despite the fact that this method was being developed during this study of 100 consecutive cases of upper gastro-intestinal bleeding, the data indicate that the method is a valuable adjunct in the treatment of upper gastro-intestinal hemorrhage.

While the data suggest that thrombin and buffer is useful in controlling hemorrhage from the upper gastro-intestinal tract, our experience leads us to the conclusion that it should not be considered as a sole form of therapy. In many cases this treatment is ineffective for stopping bleeding and in such cases early operative intervention is necessary.

The procedure is important as an aid in differentiating those patients in whom the hemorrhage is controlled from those who require surgical intervention to stop the hemorrhage. The use of the method in conjunction with the Patton tube has been useful in determining whether a patient is bleeding from the esophagus or from below the cardia of the stomach.

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DISCUSSION—DR BYRNE M. DALY, Detroit. I would like to thank the Association for the privilege of participating in this meeting. We are often asked concerning preparation of the buffer solution. This solution is made by dissolving 20.4 Gm of disodium phosphate in a liter of water, and 1.95 Gm dihydrogen potassium phosphate in 100 cc of water. It is done in this manner because of solubility. They are mixed, producing 1100 cc of seventh molar phosphate buffer with a pH of 7.6. We prefer to use this buffer.

because of its availability, non-toxicity and the fact that it is a clear solution enabling us to evaluate when bleeding has stopped. Other substances may be used such as sweet milk, soda bicarbonate and the commercial antacids, but we have found that the buffer is more effective (slides)

In determining the effect upon patients we have studied 35 hospitalized patients. This slide represents what we consider between the best and poorest results in this study. We first aspirated the contents to determine the pH by the Beckman glass electrode and in this case it was just a little above 2. At this point 30 cc of buffer were given and five minutes later the pH was determined, you can see the marked rise. At this point about 180 units of topical thrombin was administered in 30 cc of buffer and the pH and the units of thrombin were determined at five minute intervals, with results as seen.

Our treatment, as mentioned in the paper, varies somewhat. Our latest addition, which we hope will decrease mortality even more, is the addition of a Patton tube. This tube, as you see, is approximately 3 feet in length. It has three air vents, two of which are utilized, one air vent goes directly to the first balloon, the second goes to the larger one, and there is a complete lumen through the tube which allows aspiration of the stomach. In cases of suspected esophageal varices the tube is placed through the nose down into the stomach and the first balloon is dilated. The balloon is then pulled back against the cardia of the stomach and the second balloon is inflated, which will be in the esophagus, and we can tell whether this is adequately placed by applying traction, if the first balloon is not steady the tube will be pulled back. If it is firmly fixed the tube is taped at the nares. If bleeding stops after inflation it can be assumed to be from esophageal varices. If aspiration shows continued blood loss, the source can be suspected to be below the esophagus, and thrombin treatment instituted.

We feel that this addition to treatment will enable us to cut down the mortality in our next 100 cases.

AN APPRAISAL OF PANCREATODUODENAL RESECTION A FOLLOW-UP STUDY OF 61 CASES*

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AND

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THE OPERATION of pancreatoduodenal resection has been performed for 13 years, since it was first reported by Whipple¹ and associates in 1935. Large numbers of patients have been operated on during this period. Their course has been followed for a sufficient time to permit evaluation of the procedure when employed for carcinoma of the head of the pancreas, carcinoma of the ampulla, carcinoma of the duodenum and carcinoma of the lower end of the common bile duct. The operation as described by Whipple was the first attempt to apply the general principles of radical cancer surgery to these serious and relatively inaccessible lesions. A few large series of cases have been reported by Whipple,² Orr,³ Waugh and Clagett,⁴ Waugh,⁵ Bartlett⁶ and Cattell.⁷

In the six-year period from August 1942 to August 1948, 165 patients with carcinoma in the region of the head of the pancreas were observed at the Lahey Clinic, and on 56 of these a pancreatoduodenal resection was performed. During this time five additional patients had pancreatoduodenal resections for benign disease, giving a total experience for pancreatoduodenal resection of 61 cases. Careful follow-up studies have been made on every one of the resected cases.

Based on our data on a review of this experience, we have attempted to answer certain logical questions that have arisen, which can be stated as follows: (1) What patients are suitable for resection? (2) Should a one-stage or a two-stage operation be employed? (3) Is it essential to anastomose the pancreatic duct? (4) Can carcinoma of the ampulla be cured? (5) Is it worth while to resect carcinoma originating in the head of the pancreas? (6) Can a reasonable operative mortality be obtained? (7) Does pancreatoduodenal resection offer sufficient palliation in extensive cases to be worth while?

Too few series of cases have been followed for the generally accepted period of five years to judge curability on this basis. In our own series, only 12 patients were operated on more than five years ago. Orr,³ in 1945, collected 103 cases from the literature including 11 personal cases, and of this group found that no patient survived over three years. Waugh,⁵ in reporting a follow-up study of 30 cases in which operation was performed at the Mayo Clinic reported that one patient who had had a carcinoma of the ampulla survived for three years. Bartlett⁶ reported 25 cases from the Massachusetts General Hospital and found one survival of five years.

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 9, 1948.

† Trainee, National Cancer Institute.

PANCREATODUODENAL RESECTION

From August 1942 to August 1948 at the Lahey Clinic, 165 patients with carcinoma of the head of the pancreas, ampulla of Vater, duodenum and lower end of the common bile duct were treated (Table I). Fifty-six patients were submitted to pancreatoduodenal resections, an operability rate of 34 per cent. During this time two additional patients with carcinoma arising in a hyperfunctioning pancreatic adenoma were submitted to local resection. These two patients have previously been reported on by Allan and Marshall⁸. Most of the remaining patients had exploratory laparotomies and palliative procedures such as cholecystojejunostomy.

TABLE I—*Pancreatoduodenal Resection—Operability (1942-1948)*

Patients with carcinoma	165
Pancreatoduodenal resections	56 (34%)
Local resections	2

Fifty-six cases of pancreatoduodenal resection for carcinoma were divided according to the location of the lesions (Table II). In 20 the lesion arose in the ampulla. In two the lower end of the common duct was the primary site, while four had a primary lesion of the duodenal mucosa near or about the ampulla of Vater. A somewhat larger number, 30, apparently arose in the head of the pancreas, usually thought to be in the duct of Wirsung. In this latter group the process was frequently diffuse, making the point of origin impossible to determine. Three patients are submitted to pancreatoduodenal resection with an operative diagnosis of carcinoma of the head of the pancreas, in these the lesion was found to be benign. These patients were excluded from the group of 56 operated on for carcinoma and included in the five operated on for benign disease. The other two were operated on with the diagnosis of benign disease.

TABLE II—*Pancreatoduodenal Resection—Pathology*

Carcinoma of ampulla	20
Carcinoma of head of pancreas	30
Carcinoma of duodenum	4
Carcinoma of common duct	2
Total	56

Among the patients submitted to resection were both favorable and unfavorable cases. Particularly in our earlier experience, some extensive carcinomas of the head of the pancreas were included in which it was known at the conclusion of the operation that all the malignancy was not excised. These included patients with involvement of the superior mesenteric vessels, invasion of the portal vein and retroperitoneal extension. Regional node involvement, likewise, was frequently demonstrated, particularly at the inferior angle of the common bile duct and the duodenum, as well as those nodes superior to the duodenum in the gastrohepatic omentum. Our experience with these cases of more extensive malignant disease has been unsatisfactory and led us to discontinue resection in

these unfavorable cases. It is now our opinion that when local invasion or metastases to lymph nodes are present, operation should not be advised.

The operation of pancreatoduodenal resection may be done in one or two stages. Whipple,^{1, 2, 9, 10} in his extensive experience, began with a two-stage operation and now feels that the one-stage operation can be done. Trimble,¹¹ Orr,⁸ Waugh⁵ and Brunschwig¹² likewise favor the one-stage operation. In our experience with 61 pancreatoduodenal resections (Table III), at the Lahey Clinic, 25, or 40 per cent, were done in one stage. This includes all five resections for benign lesions. Thirty-six patients, or 60 per cent, were operated on by a two-stage operation, 10 of these having had their first stage done elsewhere. The first-stage operation which we recommend is a cholecystojejunostomy utilizing a long antecolic loop of jejunum. The second stage is

TABLE III—*Pancreatoduodenal Resection—Operation*

One stage operation (including 5 benign)	25 (40%)	4 deaths
Two stage operation*	36 (60%)	5 deaths
Total	61	
* 10 patients had first stage done elsewhere		

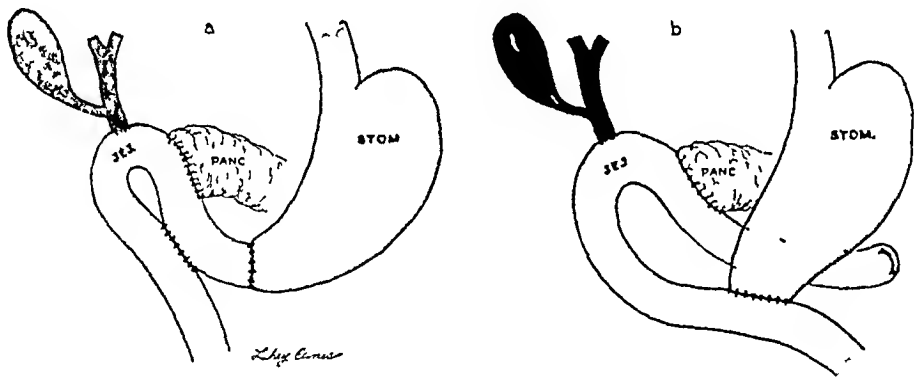


FIG 1

delayed for from two to three weeks, during which time the condition of the patient greatly improves. In our experience, this procedure does not add appreciably to the technical difficulties of the resection. We believe that the employment of the two-stage operation has enabled us to extend the operation to patients who would not otherwise be suitable risks for such a major procedure. Furthermore, it permits surgeons who do not choose to carry out the radical procedure to perform a first-stage operation at the time of their exploration. From our own experience, we believe that the employment of the two-stage operation has been the most important factor in maintaining a low mortality.

The two-stage operation is employed in patients with long-standing jaundice, in those with marked enlargement of the liver and in the group represent-

ing the poorest surgical risks. If the gallbladder has previously been removed or is unsuitable for the anastomosis, choledochostomy is satisfactory for a first stage. It adds considerably to the technical difficulty of the resection, but may be the wise procedure.

The technic of operation will not be presented in this paper. The operation that we usually employ has recently been presented¹³. The one-stage operation which we prefer has all anastomoses in an antecolic position and they consist of

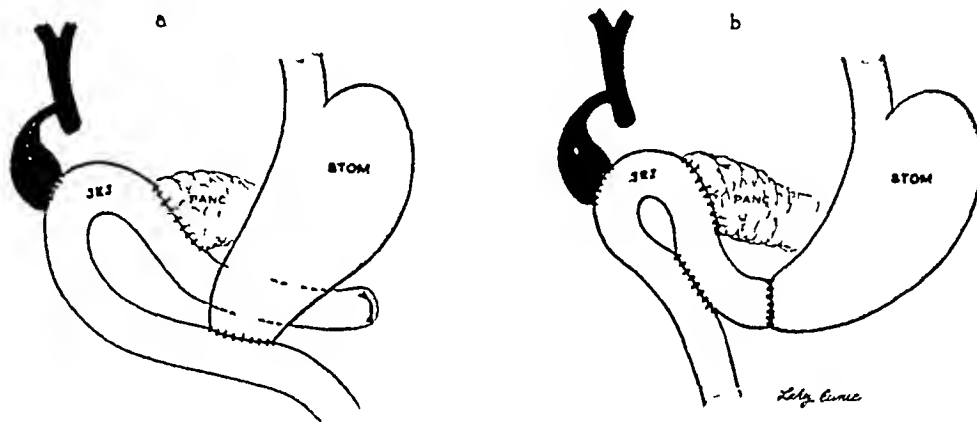


FIG 2

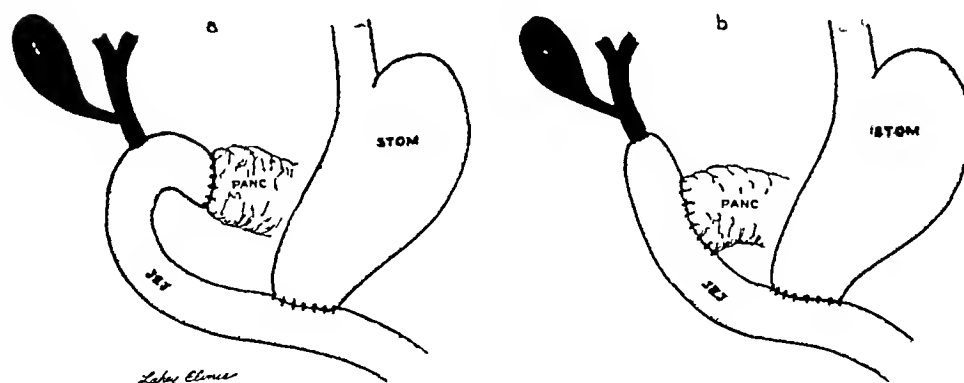


FIG 3

end-to-end gastrojejunostomy, entero-enterostomy, pancreatojejunostomy and choledochojejunostomy (Fig 1 b). The entero-enterostomy may be avoided by implantation of the stomach distal to the pancreatic and biliary anastomoses and then become an end-to-side gastrojejunostomy (Fig 1 a). In the two-stage operation, the common duct is turned in (Fig 2 a and b) or if its division is close to the entrance to the cystic duct, it is implanted in the jejunum beside the cholecystjejunostomy. Anastomosis of the end of the jejunum to the common

duct with implantation of the pancreas and stomach below the biliary anastomosis, as employed by Whipple and Waugh, has been utilized (Fig 3 *b*) This may be reversed so that the end of the jejunum is joined to the pancreas (Fig 3 *a*)

The operative mortality following pancreaticoduodenal resection has varied in the reported series from 11 to 45 per cent In the 56 resections for carcinoma in our series, there were eight deaths, a mortality of 14.3 per cent In addition to this, there were five resections for benign disease, with one death, or 20 per cent This one death occurred in a patient who was operated on with the mistaken diagnosis of malignant disease In Table IV the operative deaths are recorded, based on the site of the lesion Of the nine patients who were submitted to resection for carcinoma of the ampulla in one stage, there were

TABLE IV—*Pancreaticoduodenal Resection—Operative Mortality*

	Cases	Deaths	Per Cent
1 stage carcinoma ampulla	9	0	
2 stage carcinoma ampulla	11	1	
	<hr/> 20	<hr/> 1	<hr/> 5.0
1 stage head of pancreas	9	3	
2 stage head of pancreas	21	2	
	<hr/> 30	<hr/> 5	<hr/> 16.7
1 stage carcinoma duodenum	1	0	
2 stage carcinoma duodenum	3	2	
1 stage carcinoma common duct	1	0	
2 stage carcinoma common duct	1	0	
	<hr/> 6	<hr/> 0	
Total	<hr/> 56	<hr/> 8	<hr/> 14.3

no deaths Eleven had a two-stage operation, with one death In the total series of 20 patients with carcinoma of the ampulla, there was one death or a 5 per cent mortality It must be remembered that these are the most favorable lesions

There were nine patients with carcinoma of the head of the pancreas who had resection in one stage with three deaths, and 21 were done in two stages with two deaths, a total of 30 with five deaths, or a mortality rate of 16.7 per cent Four patients with carcinoma of the duodenum had resection, with two deaths These occurred in the three patients submitted to a two-stage operation A one- and a two-stage operation were each done for carcinoma of the common duct, without a fatality

In the interpretation of these results it should be appreciated that the patients who were the most serious risks, those with the greatest interference with liver function, were operated on in two stages We feel that this mortality rate of 14.3 per cent for malignant disease, 14.8 per cent including benign disease, is evidence in favor of a two-stage operation for the deeply jaundiced individual

PANCREATODUODENAL RESECTION

The causes of death in fatal cases are seen in Table V. Fatal gastrointestinal hemorrhage occurred in two. The site of bleeding could not be determined. Generalized peritonitis was found in two patients. In one the pancreatic anastomosis had separated. In this patient, metastases were found in the retroperitoneal region and also in the lungs. One patient died of surgical shock with possible transfusion reaction; this was the patient who had resection with a mistaken diagnosis of cancer. One of the patients early in the series died as a result of sepsis with liver abscess occurring nine weeks after operation.

TABLE V—*Pancreatoduodenal Resection—Fatal Cases*

Gastrointestinal hemorrhage	2
Peritonitis	2
Liver abscess	1
Shock	1
Hepatorenal syndrome	1
Cerebral thrombosis	1
Coronary thrombosis	1

Death followed one-stage resection in a case with an hepatorenal syndrome and associated renal suppression. The cause of death in another was cerebral thrombosis in a poor-risk patient with arteriosclerotic heart disease and hypertension. Coronary insufficiency and thrombosis caused death during operation in a 77-year-old man with a favorable lesion of his ampulla.

The duration of life following the onset of cancer in the region of the head of the pancreas is quite short. In an earlier report,¹⁴ we found in 56 consecutive patients who were operated on prior to 1935, in whom cholecyst-jejunostomy was performed, that 75 per cent were dead within six months of

TABLE VI—*Pancreatoduodenal Resection—Five-year Survival, 1942-1943*

1942	2	1*	6 years 2 months
1943	10	2*	5 years, 7 months
Recurrent Cases			
1 (carcinoid)			lived 4 years, 7 months
1*			lived 3 years 4 months
1*			lived 3 years 2 months
50% (6) lived 3 years or more			
25% (3) living and well			
* Carcinoma of ampulla			

the operation. A review of our patients submitted to pancreatoduodenal resection definitely demonstrates that life can be prolonged when the operation is performed in suitable cases and that some patients may be cured. Only a small group in this series was available for a five-year follow-up study. During 1942, two resections were done, and during 1943, 10 resections were performed, making a total of 12 patients whose course has been followed for five years. One patient with carcinoma of the ampulla is living and well after six years and two months, the second is in good condition for five years and seven months, and a third, five years and five months after operation. All had adeno-

carcinoma of the ampulla of Vater without extension. Of the patients who had recurrent disease and subsequently died, one who had carcinoid of the ampulla lived four years and seven months and two others with carcinoma of the ampulla without metastases lived three years and four months and three years and two months, respectively. Thus, in this small series of 12 cases, three, or 25 per cent, of those submitted to resection five years or more ago are living and well, while six, or 50 per cent, lived three years or more.

It seems worth while to report the three-year survival rate in our series. For the years 1942 to 1945, 27 of the 56 patients had resections. Of these, eight, or 30 per cent of the group, lived three years or more. The two patients with carcinoma of the duodenum surviving resection lived two years and eight months respectively. The two with carcinoma of the common duct, lived three years and five months and one year and nine months, respectively.

There were 30 patients with carcinoma of the head of the pancreas submitted to resection, with five fatalities. This left 25 patients, all of whom have

TABLE VII—*Pancreatoduodenal Resection—Three-year Survival, 1942-1945*

1942	2	1
1943	9	5
1944	6	0
1945	10	2
1942-1945	27	8 (30%)

had follow-up studies. Eighteen were found to be dead of recurrence, with an average duration of life of 11 months after resection. The longest duration of life was 19 months. Seven patients are still living, as follows: three years and seven months, two years and three months, one year and three months, one year, and three patients have been followed for less than one year.

This relatively short survival time after pancreatoduodenal resection for carcinoma of the head of the pancreas is the most discouraging finding in all of our experience with these cases. It is a similar observation to that of the other recorded series. It must be admitted that no patient with carcinoma of the head of the pancreas has yet been cured or survived five years or more. While many of these patients have a smooth recovery and are quite comfortable for a number of months, the duration of their life following resection hardly justifies such a major procedure since satisfactory palliation might have been procured by a sidetracking operation, such as cholecystjejunostomy, for the relief of obstructive jaundice. In the light of our present experience, we must modify the operative procedure or abandon radical surgery for carcinoma of the head of the pancreas. We have observed rapid peritoneal dissemination with carcinomatosis in patients in whom the line of resection passed through malignant tissue, and it is quite possible that in some unfavorable cases we have hastened death rather than delayed it. We can certainly assume that resection for extensive cases of carcinoma of the head of the pancreas or those with local direct extension or regional metastases should no longer be consid-

ered for resection. Even with apparently very favorable lesions confined to the duct of Wirsung, we have seen recurrence as early as nine months. An isolated observation by Cole¹⁵ may explain early recurrence with favorable lesions. He found malignant cells free in the obstructed duct of Wirsung and it is possible that dissemination of cancer occurs by cutting across the duct, with the escape of pancreatic fluid. Before discontinuing radical pancreatectomy for carcinoma of the head of the pancreas in favorable cases, we wish to suggest the employment of total pancreatectomy in which this possible complication could be avoided. It has not yet been employed under these circumstances in our clinic. According to our present understanding of this problem, the employment of total pancreatectomy in early carcinoma of the head of the pancreas offers the only chance of a possible improvement of these results.

We have undertaken a survey of the nonfatal complications as well as physiologic studies on patients after resection but these will not be reported in this paper. An excellent study of 10 cases has been recently reported by Wollaeger¹⁶ and others.

From our experiences with 61 pancreatoduodenal resections, including 56 for carcinoma, and five for benign disease, the following points have been answered: (1) The operation is technically feasible as it has been developed. (2) With proper selection of cases and the employment of a two-stage operation in selected cases, the operative mortality can be maintained at a reasonable level, one similar to that for other gastro-intestinal cancers. (3) Physiologic functions so far as the gastro-intestinal tract and pancreatic and liver function are concerned can be established and maintained. (4) Carcinoma of the ampulla can be cured in an appreciable number of cases. (5) Pancreatoduodenal resection should be confined to favorable lesions. (6) Carcinoma of the head of the pancreas has not yet been cured. (7) The operation of pancreatoduodenal resection as now employed is suitable for carcinoma of the ampulla. Pancreatoduodenal resection for carcinoma of the head must be modified or discarded.

CONCLUSIONS

A series of 61 pancreatoduodenal resections performed at the Lahey Clinic has been reported. Fifty-six were employed for carcinoma in the region of the pancreatoduodenal area and five were performed for benign disease.

Twenty patients with carcinoma of the ampulla were operated on, with one death, a 5 per cent mortality. Thirty patients with carcinoma of the head of the pancreas had resections, with five deaths, a mortality rate of 16.7 per cent. Fifty-six resections for carcinoma were done, with eight deaths, or 14.3 per cent. Five resections for benign disease were done, with one death, 20 per cent. Sixty-one resections were followed by nine operative deaths, 14.8 per cent.

Twenty-five patients, 40 per cent, had pancreatoduodenal resection as a one-stage procedure. Thirty-six, 60 per cent, were operated on in two stages.

Of 27 patients having pancreatoduodenal resections for carcinoma, eight (30 per cent) survived three years or more

Of 12 patients followed for five years or more, three show no evidence of recurrence. All had carcinoma of the ampulla of Vater. The longest period a patient was followed was six years and two months.

Pancreatoduodenal resection should be reserved for those patients with favorable lesions.

Carcinoma of the ampulla may be cured by pancreatoduodenal resection.

Carcinoma of the head of the pancreas has not been cured by pancreatoduodenal resection. A more extensive operation, such as total pancreatectomy, should be carried out or resection for this condition should be abandoned.

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DISCUSSION—DR. MALCOLM THOMPSON, Louisville, Ky. One of my medical friends has said that his most fervent prayer is to be delivered from a surgeon who is always talking about his one case. As Doctor Cattell has shown us, follow-up reports of seven years' duration upon cancer of the ampulla of Vater are infrequent, so I will risk my friend's censure and solicit your indulgence by being brief (slides).

PANCREATODUODENAL RESECTION

This shows a photomicrograph of the specimen, pronounced cancer by two pathologists, one of whom reviewed the slide a few weeks ago

This shows the method of reconstruction. The patient was in the hospital when Ridgeway Trimble's paper appeared, in the November, 1941 issue of *Surgery, Gynecology and Obstetrics*. Without the knowledge gained from his paper I am sure I would not have had the confidence to proceed. Our technic was exactly as described by him with minor changes as follows. In attempting to bring the common bile duct into the jejunum through counter incision by grasping the duct with a hemostat, the wall was so fragile that it tore, so two guide sutures were placed in each lateral wall of the duct. These were brought through a small incision into the jejunum on needles. The needles then pierced the jejunal wall a slight distance from the opening and the sutures tied upon the serosal surface. In this manner the common duct was anchored into the jejunum as shown. There was not sufficient duodenohepatic ligament to buttress the area of entrance of the duct into the jejunum, so a small piece of detached omentum was sutured around the junction. Also, there was not sufficient duodenohepatic ligament to suspend the jejunum properly so, a few centimeters distally, it was suspended by two sutures to the edge of the liver to relieve tension upon the sutures anchoring the duct.

The patient was jaundiced for five weeks before operation. One-stage excision was performed on November 7, 1941. You might note the date, for had *S G & O* been late that month we would have been content with simply a palliative shunt, or perhaps later a second stage excision. He has been well for seven years and at present there are no signs of recurrence.

This color slide shows the opened specimen a few minutes after completion of the operation. As you see it is composed of the distal portion of the stomach, the pylorus and the proximal three-fourths of the duodenum. The tumor, 2 centimeters in diameter, can readily be seen at the ampulla and, posteriorly, there is a portion of the head of the pancreas with a small segment of the common duct.

The fact that this man has gone for seven years without chills or fever, without jaundice, without any major digestive disturbances and with the biliary anastomosis distal to the gastric and no attempt to implant the duct of Wirsung will, I am sure, be of interest to Doctor Cattell and to others of you who by your originality and large experience have contributed so much to treatment of this condition.

DR RICHARD B CATTELL, Boston (closing). This is a most excellent result in the case reported by Doctor Thompson, and is a long period of survival in carcinoma of the ampulla. I am sure he is wise in recording this striking result with a seven-year survival, because there are too few long follow-ups in these cases.

RESULTS OF TREATMENT OF PATIENTS WITH HYPERTENSION BY TOTAL THORACIC AND PARTIAL TO TOTAL LUMBAR SYMPATHECTOMY, SPLANCHNICECTOMY AND CELIAC GANGLIONECTOMY¹

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ESSENTIAL HYPERTENSION or hypertensive vascular disease is by common usage a term applied to a large group of patients having elevation of systolic and diastolic blood pressure. Cause of hypertension in these patients cannot be explained by known clinical or laboratory diagnostic methods. Damage to the arteries supplying the brain, the heart, the kidneys and other organs or abnormal function of these organs is seldom evident in early stages of the disease process.

Patients who present themselves when blood pressure is moderately elevated and before occurrence of serious vascular or organic damage usually are treated by medical methods including restriction of physical and emotional activity, reassurance, sedation, reduction of weight and various drugs or diets. They must be examined periodically to determine whether or not blood pressure levels increase, vessels of the retina evidence vascular damage or renal or cardiac function alters. Eventually, serious complications occur in many.

Patients who present themselves late in the hypertensive disease process evidencing serious organic damage may also be treated by a medical program, although in some at least, delay during conservative treatment may permit rapid occurrence of complications. Eventually, most patients with hypertension die of the disease. Usually at some stage physician and patient alike consider the possibility of supplementing medical treatment by sympathectomy.

Decision regarding indications for sympathectomy is difficult because of the variety of opinions regarding the cause of hypertension and the effect of various treatments. A variety of possible etiologic factors has been developed experimentally. Contributions of many investigators have been previously reviewed and acknowledged.¹⁻⁴

Most of these etiologic factors should not be amenable to sympathectomy. The renal factor is one of these. It consists of a vasoconstrictor and vaso-pressor substance, angiotonin (Page) or hypertensin (Houssay), circulated through the blood as a result of liberation of renin during renal anoxia. This

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enzymatic humoral process apparently explains the Goldblatt hypertension produced by constricting renal arteries. Many experiments indicate that neither production nor action of this substance would be altered by sympathectomy. Another factor, arteriolar sclerosis, developing as a result of some unexplained degenerative or metabolic process, would not be directly altered by denervation of blood vessels.

Another possible etiology, neuroendocrine in nature, has been attributed to two similar sequences. One, Selye's excessive adaptive reaction,⁵ postulates stimulation in the sequence of frontal lobe, anterior pituitary and adrenal cortex, with production of excessive corticoid hormone. The other, Hembecker,⁶ postulates that functional influences stimulate the frontal lobes, which in turn affect the hypothalamic nuclei, neural hypophysis and anterior pituitary eosinophil cells, producing an excess of a cortical hormone. These in turn might constrict efferent glomerular renal arterioles, producing renin which, with anterior pituitary and cortical hormones, might cause hypertension. Either sequence is assumed as a complete chain of neurohumoral reactions independent of the sympathetic nerves. Hembecker suggests, however, that epinephrin liberated as a result of the activity of the sympathetic nerves supplying the adrenal medulla might increase the irritability of the frontal lobes and thus augment their reaction to functional influences.

Several recent developments have suggested additional causes of hypertension. Schroeder⁷ has described a pressor substance from human blood, more active in hypertensive than in normal patients. Shorr⁸ has described a balance between a vasoexcitatory material (V E M) and a vasodepressor material (V D M), originating respectively from kidney and liver, which modify vascular response to epinephrin and might, if not properly balanced, be a factor in hypertension. Shipley, Helmer and Kohlsteadt⁹ report a vasopressor substance occurring in hypotensive cats which gives a sustained increase of blood pressure in nephrectomized animals and seems different from renin.

Any of the several etiologic factors described above, if present in a patient with hypertension, would presumably weigh against a decision for sympathectomy. Experiments, however, with the Heymans' neurogenic hypertension produced by excision of the carotid sinuses and division of the cardio-aortic depressor nerves indicate that if a counterpart exists in a hypertensive patient, treatment by sympathectomy would be effective. Studies of this form of experimental hypertension and review of experiments by others¹⁰⁻¹² indicate that either splanchnicectomy or upper thoracic sympathectomy alone does not appreciably alter the hypertension, but that total sympathectomy does. Moreover, even after total sympathectomies in dogs, hypertension may partially return as some regeneration of nerve occurs. Because of the encouragement offered by these experiments and with a concept that a neurogenic etiologic factor might be present in essential hypertension, total sympathectomy in patients was attempted through a transthoracic approach in May, 1940.¹³ The celiac and stellate ganglia were included in the sympathectomy to insure completeness of visceral denervation and to minimize regeneration. Although

complete denervation, as judged by sweating tests, was not obtained, results have led to the continued use of the procedure

It is possible that, of the several etiologic factors presented above, the neurogenic factor might initiate and perpetuate the disease process in some patients, arteriolar sclerosis, renal, neuroendocrine and other mechanisms occurring later. Also, it is entirely possible that additional factors now receiving only a little attention or now unrecognized may further complicate the complex disease process

Decision regarding indications for sympathectomy in patients with hypertension is also difficult because of the difference in methods of studying and reporting results and the variety of operations employed. Methods of reporting results of sympathectomy for hypertension have varied widely, many authors changing method or operative technic frequently. Results in patients followed for several years are seldom quoted

Operations are of two general types. The first is the splanchnicectomy. Its development, including anterior root ramisection, 1930, Adson and Heuer, subdiaphragmatic approach to sympathetic nerves and branches, 1932, Craig and Adson, supradiaphragmatic approach, 1933, Peet, celiac ganglionectomy, transabdominal approach, Crile, lumbodorsal approach, 1938, Smithwick, and transthoracic approach, 1940, Grimson, has been reviewed, comparing the results of procedures and acknowledging the opinions of authors.⁴ Since this review, Poppen,¹⁴ 1947, further modified the thoracolumbar approach by resecting part of the seventh rib to gain access to the sympathetic chain as high as the fourth thoracic ganglia. Regardless of the upper level of interruption of the sympathetic nerves to somatic segments of the body, significant denervation of viscera is accomplished by each of the above operations only in the splanchnic area. Cardiac, pulmonary, cerebral, upper thoracic, arm and head areas remain supplied by sympathetic nerves from the stellate and remaining upper thoracic ganglia. The second type of operation for sympathectomy, total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy, using a transthoracic approach, 1940, Grimson,¹³ denervates thoracic viscera, head, neck, arms and chest, as well as abdominal viscera supplied by the splanchnic nerves and, to a varying extent, lower abdomen, groin and legs

In spite of the confusion described above concerning etiology, operative results and technic, most physicians today accept sympathectomy. Decision regarding indication or contraindication for surgery and type of sympathectomy is usually left to the surgeon and is a matter for individual judgment. Our experiences with splanchnicectomy performed in 45 patients of another series have led to an opinion in agreement with that of Findley¹⁵ and others that although results are occasionally excellent, usually they are temporary or poor. Also, it seems evident that the effect of this procedure is largely one of palliation. It is the purpose of this paper to present results of adding denervation of thoracic viscera, upper body, head, neck and limbs to splanchnicectomy that

surgeons may consider how results of this near total sympathectomy compare with those obtained by various forms of splanchnicectomy.

Material Operations to be reported were undertaken for 113 patients treated between June, 1940, and May, 1948. Each had a persistent elevation of systolic and diastolic blood pressure, not decreasing with medical treatment and not significantly decreasing during a week or more of hospital study preceding operation. Major complications of hypertension present before operation were hemiplegia in 19 patients, hypertensive retinopathy with hemorrhages and exudates in 38 and with papilledema in 11, definite decrease of renal function in 9, marked enlargement of the heart in 15 and definite abnormality of the heart as judged by electrocardiogram in 65. No patient had infarction of the myocardium and there was only one elevation of nonprotein nitrogen, since these were considered contraindications to operations. Also, no patient had a hypertension considered mild or not progressive by medical consultants. Ages varied from 15 to 50 years, the average was 36. There were 46 males and 67 females.

Only two patients did not have symptoms attributable to hypertension. Symptoms occurring in the remainder were occasional headache only in 11, mild headaches, fatigue, dizziness, dyspnea, blurring of vision, palpitation, precordial pain or nervousness in 23, and severe multiple symptoms in 77. It should be emphasized that each of these patients had a moderately severe or severe form of hypertension. They were selected for operation when recommended by majority opinion of consultants and not on a basis of decrease of blood pressure after sodium amytal¹² or with sympatholytic drugs¹⁶. Also, these patients usually had been followed during treatment by a medical program lasting for several years before operation, occasionally followed for about a year and only rarely for a few months.

Method of Operation Operations usually were accomplished in two stages performed three weeks apart. During each operation a lateral incision was made over the third rib, four or five inches of the rib was excised, and the upper thoracic cavity was exposed transpleurally. Through the open chest, the pleura then was incised directly over the sympathetic chain, following which dissection and mobilization of the stellate ganglion, the upper six to eight thoracic ganglia and the origin of the splanchnic nerve was accomplished. The freed chain was dropped into the lower chest and the upper incision closed. A second lateral incision was made over the tenth rib, permitting excision of six or seven inches and entry into the lower portion of the thoracic cavity. The chain and splanchnic nerve previously mobilized were picked up and freed down to the diaphragm. Here a transverse incision was made through the reflection of the pleura onto the diaphragm and through the posterior attachment of this structure. This permitted anterior and downward retraction of the diaphragm and retroperitoneal visualization of the first and often the first and second lumbar ganglia. One or both of these ganglia were removed. Traction upon the splanchnic trunk and separation of the muscular fibers of the diaphragm permitted mobilization of the greater portion of the celiac

ganglia, division of its branches and communications and partial or complete excision. Exploration of the adrenal glands, when desired, was accomplished through a small incision through the diaphragm into the retroperitoneal and periadrenal space.

Since effusion and rarely bleeding occurred after operation and since a chest drain has not caused any recognized ill effects, a stab wound was routinely made between the eighth and ninth ribs and a No. 32 Fr. Pezzer catheter brought out through it. The incision through the tenth rib bed was then closed. A sterile two-bottle, bed level to floor, gravity suction was connected to the catheter. Three weeks were allowed between this operation and the second stage, a similar procedure through the opposite chest, in order that recovery of respiratory function on the first side be fairly complete. Occasionally, patients received a third transabdominal operation to complete denervation of the lower trunk and limbs. Two patients, because of the seriousness of their disease, had bilateral transthoracic splanchnicectomies in two stages through the tenth rib followed a few months later by upper thoracic sympathectomies, also in two stages and through the fourth ribs.

The specimen of excised chain always included stellate and all twelve thoracic ganglia, splanchnic nerves, part or all of the celiac ganglia and the first or first and second lumbar ganglia.

Method of Study. Each patient was examined employing standard cardiovascular and renal techniques and observed by cardiovascular roentgenologic, psychiatric and urologic consultants. Examinations were performed during the four to ten days in the hospital before the first operation and were repeated during the second week following the last stage. With few exceptions patients were again hospitalized for four to ten days $3\frac{1}{2}$ months after sympathectomy and subsequently at yearly intervals for six years. Occasionally special examinations including blood volume, cardiac output, blood viscosity, renal blood flow and effects of posture were carried out. Details of the method of study will be given as the results are reported.

RESULTS OF SYMPATHECTOMY

Extent of denervation early and late after operation. The surface area of the body denervated by sympathectomy was determined by inspection and palpation in each patient, by Richter's neurodermometer methods¹⁷ in many and by an iodine starch heat test in 21.

The iodine starch test has been used for calculation of area of denervation. It was performed shortly after sympathectomy and again during subsequent admissions to the hospital at intervals, one to seven years later. After sweating under a heat cradle photographs were taken of the entire body, front and back. Percentages of body surface were obtained by comparing photographs with a standard surface area chart. The average of the surface area denervated in 21 patients soon after sympathectomy was 77 per cent, the range was from 54 to 98 per cent. Residual sweating after operation usually was greatest about the groin and thigh. Illustrative photographs have been published.^{2, 13} The

average of tests made one to seven years, average three years, after sympathectomy in 17 patients was 61 per cent, the range was between 39 to 85 per cent. Recovery of ability to sweat occurred in irregular patches usually on the trunk and legs and occasionally on the arms. The distribution of these patches of sweating was an irregular pattern and resembled that seen in nerve regeneration. Ray¹⁸ recently reported neurodermometer studies after "total sympathectomy" in 14 patients and described similar results. Return of sympathetic activity occurred, he attributed it to a process of readjustment taking place during the first three months after incomplete denervation. It should be recognized that sweating and neurodermometer tests record activity of cholinergic nerves distributed segmentally along with the adrenergic sympathetic fibers and supplying the body surface.

It has not been possible to test the completeness of interruption of adrenergic or true sympathetic nerves to the head, extremities or trunk or to abdominal and thoracic viscera. During operation the celiac ganglia or at least their upper and lateral portions were removed. This was done to insure the division of lesser splanchnic branches which might otherwise be overlooked and to diminish the possibility of regeneration of adrenergic vasomotor nerves to abdominal viscera. Also, the stellate ganglia were excised to insure cardiac and pulmonary denervation and to guard against regeneration. Horner's syndrome occurred bilaterally and with rare exception has persisted. Excision of these ganglia eliminates cell stations which might otherwise offer connections for myelinated preganglionic fibers growing out from rami and permitting effective regeneration and activation of unmyelinated post ganglionic adrenergic fibers.

A definite change of heart rate occurred after sympathectomy. The heart rate under basal conditions, as recorded by the electrocardiograph, averaged 76 before sympathectomy and 59 a few weeks afterward. Two to six years later the average was 58. The rates four to seven and one half years after sympathectomy showed no further recovery, the average being 58. These persistent low rates might indicate failure of regeneration to the heart.

Operative Mortality Four of the 113 patients died in the hospital shortly after sympathectomy (Table I). Three of these four deaths occurred among the first 19 patients treated, and each of the three patients exhibited findings now conventionally accepted as contraindications to sympathectomy. These operations were performed in 1940 and 1941 to test the effectiveness of the new procedure in otherwise hopeless or late stages of the hypertensive disease process. The first patient, a 48-year-old male, had all of the findings associated with malignant hypertension, including elevation of blood urea and nitrogen. He developed pneumonia two weeks after the first transthoracic operation, became uremic during treatment with sulfathiazole and died 47 days later. The second patient, a female of 33, had had a severe hypertension for 11 years, complicated by occurrence of several cerebral accidents. At the time of operation she was confined to bed. Examination revealed findings of hemiplegia, severe encephalopathy and also malignant hypertensive retinitis with papilledema.

There were recurring periods of unconsciousness before and between the two operations. Respiratory arrest occurred one day after the second stage. Blood pressure remained around 140/90 during several hours of artificial respiration just preceding death. The third operative mortality occurred in a 43-year-old male. He had had many episodes of nocturnal dyspnea. Examination of the retina revealed advanced arterial sclerotic disease and areas of venous thrombosis and macular degeneration. After the second operation blood pressure was reduced to normal for 56 hours and then respiratory arrest occurred. Autopsies of the last two patients revealed evidence of increased intracranial pressure. The arteries of the circle of Willis showed advanced sclerotic degeneration.

TABLE I—*Survival Statistics of Patients Treated by Subtotal to Total Paravertebral Sympathectomy*

Follow Up Period — 1 to 9 Years — Average 3½ Years			
Operative mortality		Ratio Living During Each Year Period	
Respiratory arrest	2		Now Living
Uremia	1	8 years plus	7 of 9
Myocardial infarction	1	7 to 8 years	2 of 8
	—	6 to 7 years	3 of 3
Total	4	5 to 6 years	3 of 4
Death since operation		4 to 5 years	7 of 9
Cerebral vascular	6	3 to 4 years	16 of 19
Cardiac	3	2 to 3 years	24 of 25
Phlebitis	1	1 to 2 years	35 of 36
Cushing's	1		—
Pregnancy	1	Total	97 of 113
	—		
Total	12		
	Total now dead	16	
	Total now living	97	
		—	
	Total number	113	

The fourth patient who died shortly after sympathectomy was a male of 37 years of age with a severe hypertension of two years known duration. During six months prior to operation he had noted "tightness in the chest" after mild exercise. This was relieved after a few minutes of rest. Two electrocardiograms revealed only left axis deviation. Death occurred on the third day after the second sympathectomy. Autopsy revealed marked arteriosclerosis of the coronary arteries. Occlusion of one artery by a fresh thrombus had caused necrosis of the myocardium. This is the only operative death occurring during the last six years or among the last 94 patients.

Survival Statistics (Table I) Twelve of the 113 patients treated by sympathectomy died during the one to eight and one-half year period of postoperative observation. Four of these twelve obtained no symptomatic improvement. Two died two months after operation with cerebral accidents and one with myocardial infarction. The fourth developed thrombophlebitis and a marked neurosis after the first stage of the sympathectomy and left the hospital. Death occurred two months later at home and cause could not be determined.

The remaining eight patients dying after the operation had described some symptomatic improvement. Two were of unusual interest. One had a diagnosis of "Cushing's syndrome" established before operation. The sella turcica was normal by roentgenogram. Sympathectomy was completed at the time of exploration of the abdomen and either side of the chest searching for tumor. Biopsy of the adrenal glands was performed during the abdominal and each transthoracic operation. After completion of the sympathectomy blood pressure remained at normal levels for one year and symptoms of dizziness, headache and palpitation were relieved. Other characteristic changes and symptoms of "Cushing's syndrome" progressed, however, even though medical treatments including roentgen-ray therapy to the pituitary gland were employed. Osteoporosis led to multiple fractures and collapse of vertebrae. Tuberculosis of the spine and later acute hematogenous milary tuberculosis then developed. Death occurred 33 months after sympathectomy. At autopsy, although the hypophysis was grossly normal, a small basophilic adenoma was found during microscopic examination. The second patient of special interest was a girl, 15 years of age at the time of sympathectomy whose blood pressure had been reduced to normal during 15 months. She then became pregnant, concealing this from the family for seven months. Convulsions then occurred and she was hospitalized elsewhere with a blood pressure of 230/160. Death occurred one day later.

Of the remaining six patients dying during the period of postoperative observation, four had cerebral accidents 14, 16, 17 and 36 months after sympathectomy. The remaining two patients died suddenly of heart failure, one 46 months and the other 26 months after sympathectomy. The last case is of interest. She had had a bilateral supradiaphragmatic splanchnicectomy one year and two months before completion of the sympathectomy and had obtained little improvement and no reduction of pressure with this procedure. There was definite clinical improvement following a three-stage paravertebral sympathectomy but no reduction of pressure. The patient was rehabilitated sufficiently to do light work until three months before death. Progressively increasing cardiac decompensation then developed. Terminally intestinal volvulus occurred. Autopsy revealed generalized sclerotic and thrombotic arterial vascular disease.

Ninety-seven of the original 113 patients are now living one to eight and a half years after operation, an average survival time of 36.5 months (Table I).

It is evident that most deaths after operation occurred among the eight patients treated seven to eight years ago. At this time the operation was employed for patients in an extremely advanced stage of the disease. Of the six patients who were operated upon during this year and subsequently died, two were operative mortalities described above, another had the "Cushing's syndrome" and the remaining three developed cerebral vascular accidents 16, 17 and 36 months after operation. In general, considering the type of patients treated, it is believed that the above survival periods are more than satisfactory.

Effect upon Blood Pressure Blood pressures were obtained at intervals

before and after operation in the office and also during periods of four to ten days in the hospital. Readings were obtained while patients were supine and usually also while sitting and standing. Generally, office readings taken in the supine position were somewhat higher than those taken routinely four times a

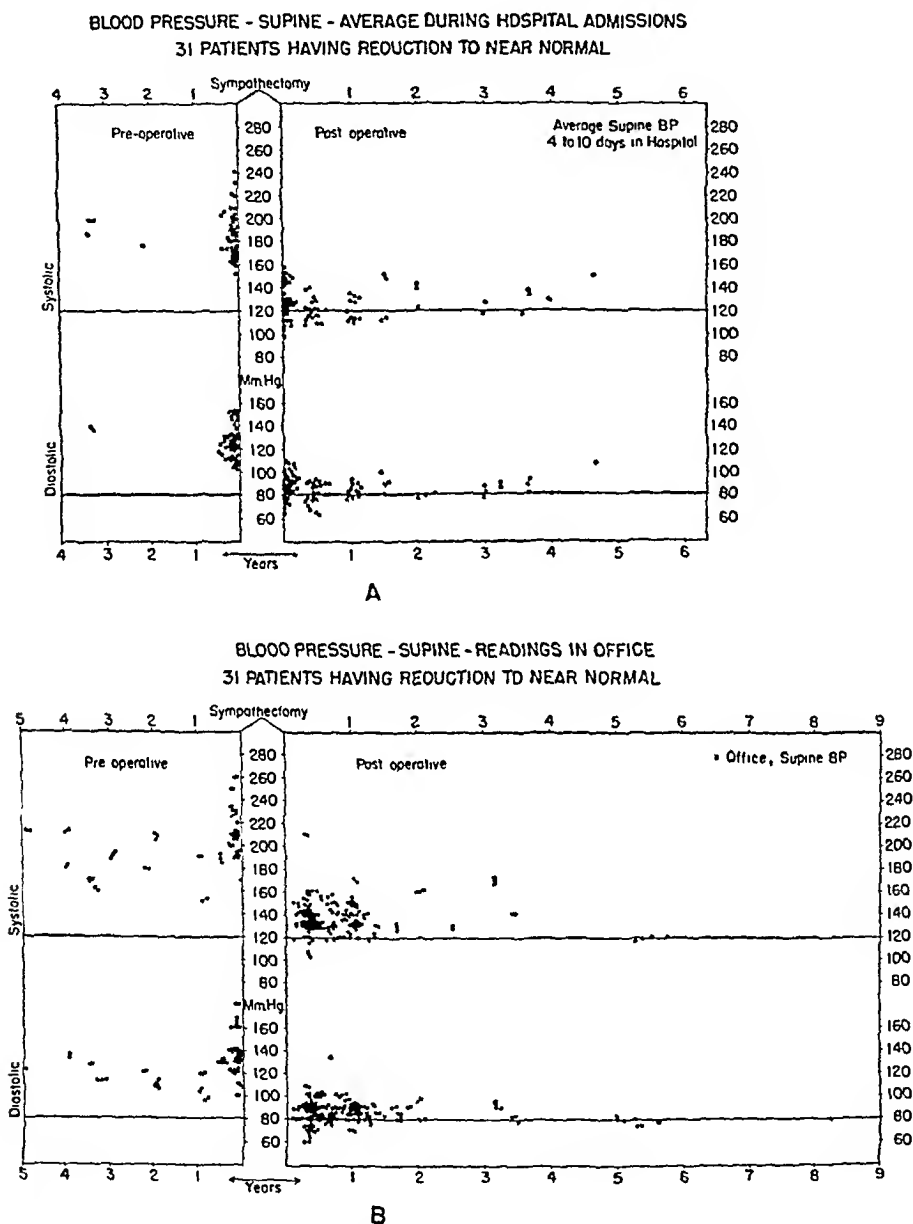


FIG 1—Scattergraphs present blood pressures of 31 patients considered as having reduction to near normal values as judged by average supine pressures during admissions to the hospital (A). Office readings of the same patients in the supine position are presented in (B). Progressive elevation of pressures during the years before operation has ceased afterward.

day during hospital admissions. After operation a postural hypotension occurred, blood pressure decreasing with upright posture and with exercise. During the first several months standing often produced dizziness. Subse-

quently, little or no dizziness occurred. The postural hypotension with few exceptions persisted during periods of observation as long as 8½ years. It was not associated with tachycardia since heart and adrenal glands were denervated.

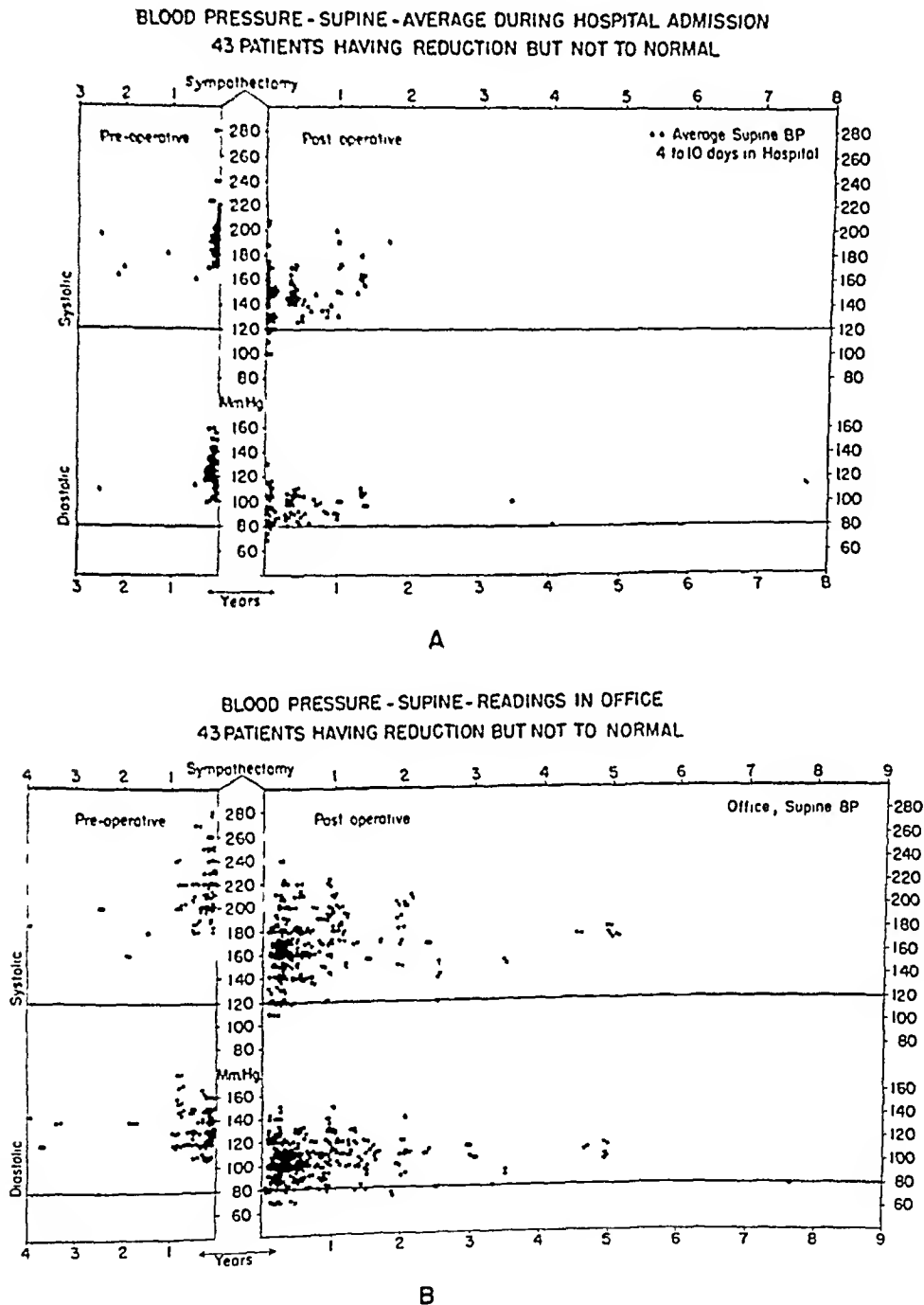


FIG 2—Scattergraphs present blood pressures of 43 patients having reduction but not to normal as judged by hospital averages (A). Office readings of these patients (B) indicate progressive increase of blood pressure before operation and a plateau during the years afterward.

Master charts plotting the course of the blood pressure were kept for each patient. Since the readings in the hospital fluctuated less than those obtained in the office, the hospital readings were chosen as the basis for determining

effect of sympathectomy upon blood pressure. Supine readings during each admission to the hospital but excluding those during cold pressor, sodium amytal and other tests were averaged and indicated as a single point on the

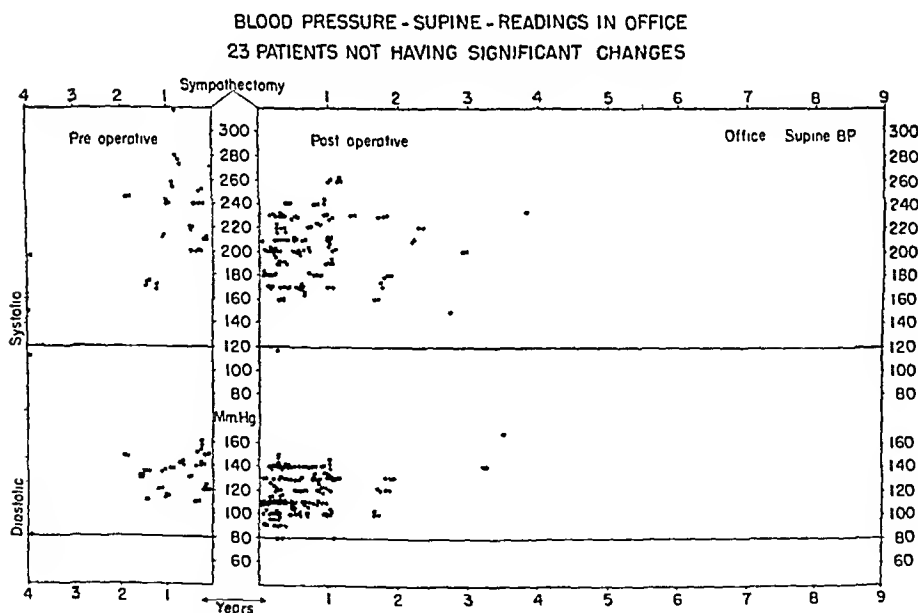
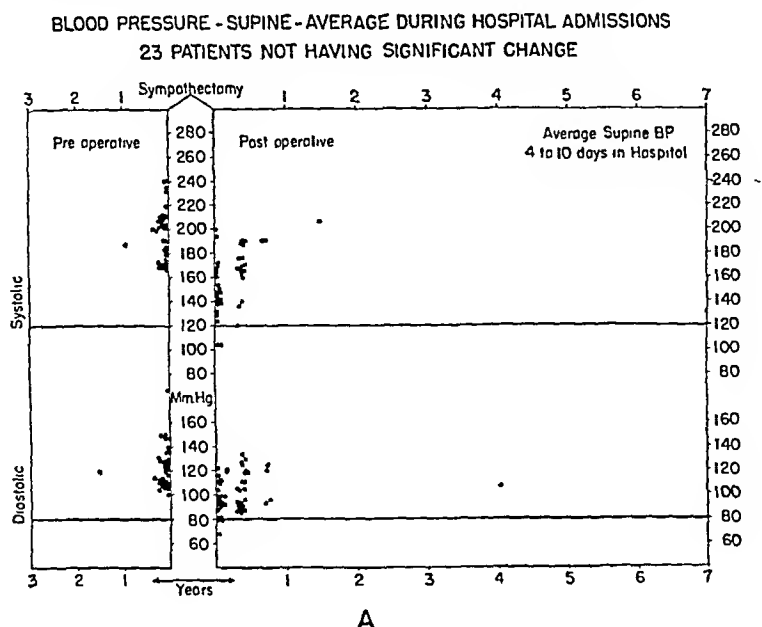


FIG 3—Scattergraphs present blood pressures of 23 patients having no significant reduction of blood pressure as judged by averages during hospital admissions (A) or readings in the office (B). Pressures during the years after operation have not increased.

patient's master chart. The master chart of each of the 97 patients now living was then surveyed to determine whether the over-all record indicated reduction of blood pressure to near normal, reduction but not to normal, or no definite reduction. On the basis of this individual survey, 31 patients were

considered as having reduction of blood pressure to near normal. For presentation, a scattergraph has been prepared (Fig 1) showing a dot for each hospital average on each patient (A) and for each office reading of each patient (B). On the same basis, 43 patients were considered as having reduction but not to normal (Fig 2, A and B). Similarly, 23 patients were considered as having no significant reduction (Fig 3, A and B). Examination of individual master charts usually reveals the same upward trend of blood pressure before sympathectomy which is evident in these scattergraphs but always the same arrest of upward trend or plateau after sympathectomy.

Age at the time of sympathectomy of the 31 patients with near normal blood pressure presented in Figure 1 varied from 17 to 46 years, average 32. The age of patients in Figure 2 with reduction but not to normal varied from 20 to 48, average 38 years. The age of patients without significant reduction (Fig 3) varied from 27 to 50, average 38 years.

TABLE II—Symptoms Before and After Sympathectomy 97 Patients Now Living

	Nervous- ness	Blur- ring Vision	Fatigue	Dizzi- ness	Head- aches	Pre- cordial Pain	Palpi- tation	Dyspnea
Number of Patients								
A Before operation								
1 31 with B P reduced to normal	13	13	8	15	28	10	11	18
2 43 with some reduction	18	14	16	29	41	11	20	18
3 23 with no reduction	8	9	9	11	20	12	13	15
	—	—	—	—	—	—	—	—
Total 97 patients	39	36	33	55	89	33	44	51
B After operation								
1 31 with B P reduced to normal	0	1	8	11	6	0	1	3
2 43 with some reduction	3	5	8	14	16	3	0	8
3 23 with no reduction	4	5	7	5	13	1	2	8
	—	—	—	—	—	—	—	—
Total 97 patients	7	11	23	30	35	4	3	19

Known duration of hypertension among the 31 patients with blood pressure reduced to near normal varied from 1 to 10 years, average 5.1, of the 43 with some reduction, 0 to 20 years, average 6.7, and of the 23 with no reduction from 2 to 17 years, average 7.8. Average duration of symptoms in the three groups was consecutively 4.6, 6.7 and 6.8 years. During the remainder of this paper results of sympathectomy will be presented separately for each of the three groups.

Effect upon Symptoms of Hypertension Symptoms attributable to hypertension occurred before sympathectomy in all but two of the 97 surviving patients. With rare exceptions, symptoms when they occurred after operation were much less severe. Incidence of symptoms is recorded in Table II.

It is evident that the number of patients relieved of symptoms is greatest in the group with most reduction of blood pressure and least in the groups with less or no reduction. Exceptions to this observation occur in the column under precordial pain and palpitation. These two symptoms, occurring in 33 and 44 patients, respectively, before operation, were relieved in all but 4 and 3 after-

ward Since the operation interrupts both nervous pathways conducting pain from the heart and sympathetic cardiac accelerators, elimination of these complaints is expected in all cases The exceptional persistence in the few might be explained by error inherent in subjective observations Symptoms listed in Table II are those described during the first several months before operation and those during the last several months preceding this report

Effect upon Complications of Hypertension For convenience, incidence of complications of hypertension is presented in Table III Each of the five major complications will be discussed individually, adding separation into groups according to results on blood pressure

Cerebral vascular accidents with hemiplegia (Table IIIA) occurred once or oftener before sympathectomy in 19 patients Sixteen of these patients are now living, seven longer than five years Of these 16, one now living after eight

TABLE III—Complications of Hypertension

	Entire Series of 113 Patients Before Sympathectomy	Currently Surviving Series (97 Patients)		
		Preoperative	At 3 Months	Latest Observation (1 or more years)
A Cerebral accidents with hemiplegia	19	16	0	1
B Retinopathy				
1 None	73	68	78	44
2 Hemorrhages or exudates	38	29	8	1
3 Papilledema	11	5	1	1
C Enlargement of heart				
1 None	64	60	43	37
2 Moderate	34	30	38	11
3 Marked	15	7	14	11
D Abnormalities of electrocardiogram				
1 None	48	45	45	32
2 LAD only	16	13	12	5
3 T Wave and/or ST segment	27	21	21	17
4 Strain	22	18	10	5
E Diminished renal function	9	5	1	1

years has had three cerebral vascular accidents since sympathectomy but is able to be up and about although activity is restricted His blood pressure was not significantly reduced by operation Another patient apparently had a minor cerebral accident one year after sympathectomy but did not develop hemiplegia Her blood pressure also was not reduced The remaining 14 patients have not had cerebral vascular accidents since operation Of the entire group of 16 patients, reduction of blood pressure to normal occurred in five, some reduction in six, and no reduction in five

Effect upon Hypertensive Retinopathy Table III B presents the incidence of occurrence of retinal hemorrhages and exudates and of papilledema, grouping all patients together These complications of hypertension were present before operation in 40 of the 113 patients of the entire series and in 29 of the 97 now living Of the 31 surviving patients whose blood pressure remains

reduced to normal, 10 had hemorrhages and exudates before operation and three of those also had papilledema. Hemorrhages and exudates disappeared before examinations made three months after operation in eight patients. Two evidenced this complication three months after operation but not during subsequent examinations. Retinopathy has not reappeared in any of these patients. Of the 43 surviving patients whose blood pressure was reduced but not to normal only eight had hemorrhages and exudates and of these only one had papilledema. This disappeared after operation, although in three patients, retinopathy continued at three months, disappearing later. In no patient observed for longer intervals has it reappeared. Of 23 patients with retinopathy before operation and now living but not having significant reduction of blood pressure, 11 had hemorrhages and exudates and of these three also had papilledema before operation. Afterward, hemorrhages, exudates and papilledema persisted in one patient. This patient had been treated by a strict rice diet without effect before and after sympathectomy. When last observed nine months after operation he refused further diet or treatment and has subsequently refused to return for examination. He reports, however, when last contacted four years after operation, that he is well and working regularly. Another patient had exudates but no papilledema one year after sympathectomy. The exudates were described by the ophthalmologist as apparently old. They had disappeared when the patient was examined two and one-half years after operation. A third patient with hemorrhages and exudates present three months after operation has not been back for subsequent observation. With these three possible exceptions, all of the 12 patients in this group having hemorrhages and exudates present before operation and not having reduction of blood pressure afterward have had disappearance of these lesions. Also, they have not to our knowledge had recurrence.

It is evident that hemorrhages and exudates were present before operation least frequently in the group of 43 patients whose blood pressure was reduced but not to normal.

It is of interest that five patients of the 97 had marked reduction of blood pressure during the first week after their last operation and became irrational or developed coma. Three had temporary increase in blood N P N. All recovered. During this episode of presumed encephalopathy these five patients had increase of hemorrhages and exudates and mild papilledema, which later disappeared.

The above observations concerning the ophthalmoscopic appearance of the fundus in the entire series of 113 patients are based largely upon the presence or absence of hemorrhages, exudates or papilledema as obtained from patient records of two hospitals. Details of the ophthalmoscopic evaluation in the first 19 patients operated upon at the University of Chicago have been reported by Gans.¹⁰ One of us (B. A.) has examined records of the 94 patients subsequently treated at Duke University. The records of 78 of these patients were sufficiently complete so that results might be evaluated on a basis of appearance of the entire fundus rather than on a basis of occurrence of hemorrhages.

exudates or papilledema. Usually these records included personal observations or fundus photographs. He has evaluated results considering condition of discs, sheathing of vessels, changes in light reflexes and color of vessels, attenuation of arterioles as compared with veins, localized changes in caliber of arterioles or venules, increased tortuosity, accentuation of arterio-venous compression, development of epivascular pigment streaks, appearance of retinal edema, "cotton wool" patches or hard "edema residues" and occurrence or organization of hemorrhage. Rather than attempt grouping according to the conventional Keith-Wagner, Gifford, Gans or Freidenwald classifications, each of which has its definite limitations, this co-author has grouped results of sympathectomy depending upon whether the entire ophthalmoscopic appearance of the fundus revealed hypertensive retinopathy before operation, and whether if present this retinopathy improved, was unchanged or increased following operation. These groups are presented in Table IV and compared with effects of sympathectomy upon blood pressure. Included among the 19 patients with retinopathy unchanged are 15 with minimal abnormalities and four with moderate hypertensive retinopathy. Three of these four had been followed for only three months at the time of latest observation. The fourth had been followed for two years and evidenced increasing vascular change, although exudates present before operation had disappeared. The two patients showing

TABLE IV—*Effect of Sympathectomy Upon Hypertensive Retinopathy Grouped According to Effect Upon Blood Pressure (78 Patients)*

	Totals	No Retinopathy	Retinopathy Improved	Retinopathy Unchanged	Retinopathy Increased
A Blood pressure reduced to normal	24 pts	6 pts —25%	14 pts —58%	4 pts —17%	0 pts —0%
B Blood pressure reduced but not to normal	37 pts	13 pts —35%	11 pts —30%	12 pts —32%	1 pt —3%
C Blood pressure unchanged	17 pts	8 pts —47%	5 pts —29%	3 pts —18%	1 pt —6%
Total	78 pts	27 pts —35%	30 pts —38%	19 pts —24%	2 pts —3%

increased retinopathy in Table IV are the same two who had hemorrhage or exudate, and in one papilledema (Table IIIB), details of these patients have been described above.

Effect upon Renal Function. Each patient has had conventional examinations of renal function before and at intervals after operation. These always included P S P, Mosenthal or Fishberg, blood nonproteins nitrogen or urea nitrogen and often included urea clearance or urea ratio. With few exceptions, pyelograms were obtained before operation. These revealed few abnormalities. Moderate albuminuria was found in some patients, but quantitative albumin studies were not obtained.

Review of work sheets plotting results of tests of each patient before and at intervals after operation has not revealed a definite change or trend. With nine exceptions, renal function was essentially normal before operation. Review of plotted work sheets after operation for the patients with normal renal func-

tion has shown that function has not become impaired during the period of postoperative observation even in those patients who had no reduction of blood pressure and have been followed for several years. Publication of details of these tests does not seem warranted.

The nine patients differing from the others by having evidence of impaired renal function before sympathectomy will be discussed. Four had elevation of blood urea nitrogen. One of these died in uremia after the first stage of the sympathectomy, one died of respiratory arrest shortly after the second stage, two died three years afterward, one of cardiac failure and the other of a cerebral accident. The remaining five patients are now living. Each had reduced renal function as judged by several low phenol-sulphonphthalein clearances or by poor concentration of urine during several Mosenthal tests. Blood non-protein nitrogen was not elevated. Three were treated medically by sedation and a rice diet during several weeks in the hospital before sympathectomy. Diminished renal function as judged by these tests persisted in only one after operation.

Effect upon Size of the Heart As indicated in Table III C, 49 of the original 113 patients had enlargement of the heart, moderate or marked as arbitrarily judged by review of chest roentgenograms taken at six feet or in a few instances by fluoroscopy. Detailed measurements of the cardiac shadow in films and adjustment according to weight and height permitted calculation of percentages of deviation from average normal heart size in 86 patients. Using such accurate measurements when possible and other information when not possible, all patients were grouped according to whether hearts were not enlarged or were moderately or markedly enlarged. Patients grouped in Table III C as having moderately enlarged hearts had a percentage deviation from normal of plus 11 to 20 per cent. Those grouped as having markedly enlarged hearts had a deviation of plus 20 per cent or more. It is evident from Table III that of the fifteen patients having marked enlargement before operation only seven are now living.

Of the 97 patients currently surviving, 30 had moderate and seven marked enlargement before sympathectomy. It is evident (Table III C) that three months after operation the number with marked enlargement of the heart increased, occurring in 14 of 95 patients. At the time of the last observation, a year or more after operation, the number with marked enlargement remained relatively increased, occurring in 11 of 59 patients examined. The number with moderate enlargement also increased at three months but then decreased after one or more years. Explanation of this relatively poor effect of sympathectomy does not develop when results are separated into three groups according to effect upon blood pressure.

Among 31 patients now surviving with blood pressure at near normal values, cardiac enlargement was moderate in seven and marked in none before operation. Of 30 examined at three months, eight had moderate enlargement and two marked enlargement. Of 21 examined subsequently, only three had

moderate and none marked enlargement. Of 43 patients with blood pressure reduced, 16 had moderate and two marked enlargement before operation. At three months 42 patients were examined and of these 24 had moderate and three marked enlargement. Subsequently, however, of 23 examined, six had moderate and three marked enlargement. Among 23 patients without significant reduction of blood pressure, seven had moderate and five marked enlargement before operation. At three months, six of 23 patients examined had moderate and nine marked enlargement. At a year or more, 13 patients were examined and of these two had moderate and eight marked enlargement.

It is evident that for some unexplained reason the incidence of patients having either moderate or marked enlargement of heart size increased during examinations made three months after operation. It is also evident that incidence tended to decrease in later observations. The decrease, however, was definite only among patients with reduction of blood pressure to near normal. Decrease of incidence of moderate enlargement of the heart occurred among those patients with reduction of blood pressure but not to normal. Incidence of marked enlargement increased, however, and the total percentage of those with enlargement, therefore, remained little changed. Among patients with no reduction of blood pressure incidence of enlargement increased.

Effect upon the Electrocardiogram The most significant effect evident in electrocardiograms obtained before and at intervals after sympathectomy is a constant decrease of heart rate following operation. This persisted throughout the period of postoperative observation. As illustrated in Table III, a comparison preoperatively and at three months of incidence of the patients with normal electrocardiograms (D 1), those with left axis deviation only (D 2), those with this plus significant T wave and/or ST segment abnormalities (D 3) and those with definite strain patterns (D 4) reveals a marked similarity before and after operation in each of the first three categories. Only in incidence of strain pattern (D 4) was there a definite decrease. At one year or more there was a moderate decrease of incidence of left axis deviation and of strain pattern but a definite increase of the proportion of patients exhibiting T wave and/or ST segment abnormalities. Presentation of these varying effects is somewhat aided by separation of results into three groups according to effect of operation upon blood pressure.

Among 31 patients now surviving with blood pressure at near normal values, electrocardiograms were normal before operation in 20, demonstrated L A D in four, T wave changes in three and strain pattern in four. At three months, distribution was essentially the same. Of 20 patients followed for a year or more, 13 had normal electrocardiograms, one had L A D, four demonstrated T wave changes and two showed strain patterns. Incidence of abnormalities among patients surviving with reduction of blood pressure but not to normal was, before operation, 23 normal, three L A D, ten T wave abnormality and seven strain pattern. At three months and at one or more years, incidence of abnormal electrocardiograms was essentially the same, only two

improving by exhibiting change from strain pattern to T wave abnormality. Of 23 patients with no reduction of blood pressure, electrocardiograms were normal before operation in only two. L A D was present in six, T wave abnormalities in eight and strain pattern in seven. At three months, five of 20 examined had normal electrocardiograms, five had left axis deviation, six had T wave abnormalities and three showed strain patterns. Of 15 patients followed for one year or more, five had normal electrocardiograms, two showed L A D, six T wave changes and two strain patterns.

In general the above study of results of sympathectomy as judged by electrocardiogram has demonstrated little effect. Decrease in the incidence of strain pattern and other abnormalities apparent in some groups might be explained by failure of a few patients exhibiting these abnormalities to return for their examinations after a year.

Effect of Subsequent Pregnancy. Four patients became pregnant after sympathectomy. One patient, whose blood pressure had been normal during six years, delivered normally at term. Blood pressure, normal before and after delivery, rose for a few hours during labor to 180/110 but subsequently has remained normal. Another patient whose blood pressure had been normal for one year following sympathectomy, developed moderate elevation of pressure during her nine months, the highest reading being 220/140 at term. Following delivery her pressure returned to normal gradually during the next year and a half. The third patient with reduction of blood pressure to normal became pregnant during the first months after sympathectomy. Blood pressure remained normal during the first seven months of pregnancy and then rose, the hospital average at the time of delivery being 196/134. Pressures then returned to normal. This patient again became pregnant, delivering her second child a year and a half later. Hypertension reappeared during the last two months of pregnancy and remained at high levels following delivery.* The fourth patient also had reduction of blood pressure to normal for 14 months. She then became pregnant, but refused prenatal care. She is the patient (described above under survival statistics) who died of a toxemia of pregnancy with blood pressures as high as 248/180.

DISCUSSION

It is now well-established that splanchnicectomy may be an adjunct to the treatment of hypertension in certain patients. Many observers, however, feel that results following this operation are frequently poor or temporary. Results of extending sympathectomy to include the stellate and upper thoracic ganglia as well as the nerves usually removed during modern operations for splanchnicectomy have been presented in some detail so that the reader may judge whether the frequency of poor or temporary results has been decreased by this more complete sympathectomy. It is our impression, based upon experiences with splanchnicectomy in another series of patients, that this has happened.

The observations presented above apparently indicate that, with few

* Since preparation of the paper, this patient died of a cerebral vascular accident.

exceptions, progression of the hypertensive disease process has been retarded or in some patients even arrested. Also, reduction of blood pressure, relief of symptoms, prevention of recurrence of complications and elimination of hypertensive retinopathy has occurred in most patients. The only observations that have not indicated much improvement are those based upon heart size and electrocardiograms. Survival statistics seem to indicate that, considering the type of patients selected for operation, life expectancy has been increased. It must be emphasized, however, that these patients represent a selected group and that a suitable control series has not been possible. Selection has included patients under 50 years of age who do not have elevation of blood nonprotein nitrogen, hypertensive encephalopathy with increased intraspinal fluid pressure or infarction of heart muscle and who exhibit reasonably adequate emotional stability. Selection has excluded patients with mild or nonprogressive types of hypertension.

Of the various possible etiologic factors presented in the introduction of this paper, only one, the neurogenic, would explain entirely the results obtained and the apparent improvement of results over those observed or described after splanchnicectomy alone. This, unfortunately, cannot be interpreted as proving that these patients had neurogenic mechanisms as the initiating and perpetuating factor of their hypertension. Sympathectomy may have nonspecific effects resulting from denervation of the vascular bed or the viscera which might indirectly influence other hypertensive mechanisms.

Special tests of the circulation were obtained in some of the patients described above and will be discussed. They have shown that following sympathectomy total blood volume, blood viscosity and renal blood flow were not significantly altered. Details of these tests will be reported by W. Adams, A. Alving and others. Cardiac output values, determined in nine patients by W. Adams using a modification of the acetylene method, ran slightly lower after operation than before. He suggests that decrease of cardiac output approximately parallels reduction of heart rate. Cardiac output values, determined by J. Hickam employing the Fick principle and using the cardiac catheterization technic, revealed little deviation or slight reduction below normal with patients in the supine position. The moderate changes of cardiac output observed by Adams and Hickam had no relation to reduction or failure of reduction of blood pressure following sympathectomy. Hickam also observed that as blood pressure was reduced by postural changes during tilting, further reduction of cardiac output occurred. This reduction did not exceed that expected during tilting of normal patients. Also he observed that moderate exercise in the supine position in these sympathectomized patients resulted in an increase of cardiac output similar to that occurring in normal patients. Since blood volume and blood viscosity were not definitely changed in the sympathectomized patients tested and since cardiac output was little reduced, one must assume by exclusion that the total peripheral resistance was decreased following operation in those patients having reduction of blood pressure.

Results of the cold pressor test (Hines²⁰), performed on all patients before and after sympathectomy are not reported in detail since they evidently contributed little or no information relative to advisability of operation or result. Immersion of one hand in ice water usually produced prompt increase of blood pressure before sympathectomy and also afterward, even though the operation had effected denervation of thoracic and abdominal viscera together with loss of sweating of as much as 54 to 98 per cent of the body surface area.

Similarly, rest and Sodium Amytal tests¹² failed to predict the effect of sympathectomy, and results will be discussed without presenting details. Analysis of individual graphs of blood pressure readings obtained hourly during a 24-hour study period revealed that the lowest single diastolic reading reached during preoperative tests was less than the average recumbent blood pressure of the patient during the first several weeks after sympathectomy in half the number and higher in half. If the general low level during the preoperative test rather than the lowest single diastolic reading is compared with the average recumbent diastolic blood pressure during a week in the hospital one or more years after sympathectomy, then the test level is lower than the late postsympathectomy level in a little less than half the number of patients and higher in a little more than half. Analysis of these data evidently indicates that results of the Sodium Amytal tests are not significant.

The basal metabolic rate was determined in 23 patients before and after sympathectomy. Postoperative determinations were made at intervals up to four years after operation. With one exception there was a slight decrease of basal metabolic rate both shortly after operation and during tests obtained up to four years later. Since the average B. M. R. before operation was plus 4, the average several weeks afterward minus 4 and the average one to four years later only minus 11, the changes were not considered significant. Most patients gained in weight.

Blood pressure readings presented in this paper have been taken in the supine position after rest. With exercise, and particularly with erect posture, additional reduction of blood pressure occurs. This is true in all patients including those whose blood pressure in the supine position was not significantly reduced by operation. It is of interest that although before operation blood pressure increased immediately after exercise in those patients tested, afterward there was a decrease, frequently rather large, in all tested. Postural lowering of blood pressure as judged by systolic levels has persisted in all patients. As judged by diastolic blood pressure, it has persisted in most, only a few, several years after sympathectomy, having a slight increase of diastolic pressure while standing. Bradycardia effected by sympathectomy persists in the upright position. Even after exercise, such increase of heart rate as occurs seldom approaches the normal or preoperative resting rate of 70 to 80 beats per minute.

Experiences with four patients pregnant at some time after sympathectomy have indicated that hypertension may recur during this condition. Although

the new elevation of blood pressure receded following delivery in two patients, elevation of blood pressure persisted at high levels in another two, causing complications leading to death. It therefore does not seem advisable that pregnancy be recommended following sympathectomy for hypertension.

One patient treated four years preceding our latest follow-up report had his sympathectomy because of polycythemia vera and hypertension. Detailed studies of his blood were reported by Schafer²¹. They indicated definite decrease of volume and number of red blood cells following sympathectomy. Although he had been treated by withdrawing blood at frequent intervals during two years preceding operation, this has not been necessary afterward, and the patient reported after four years that he remained well. Another similar result in a second patient with polycythemia has led to the impression that sympathectomy may be recommended for some patients with hypertension and polycythemia.

Finally, it should be emphasized that near total sympathectomies are associated with certain disabilities or inconveniences. Some of these complications persist only during the first several months after operation. Of these, the most serious has been pain, which occurs in all patients and is intense in many. It has lasted in occasional patients as long as a year. Postural lowering of blood pressure occurs and usually produces disability during the first several months after operation. Symptoms of dizziness when standing rarely persist a year. Following this period of time, postural lowering of blood pressure persists but is not associated with disability. Other complications unfortunately persist, although they are somewhat less troublesome after a year or two. One of these is excessive sweating occurring in areas of regeneration or in areas not denervated. This produces inconvenience by moistening clothing, particularly during hot weather. Another persistent symptom is partial obstruction of nasal airways caused by swelling of the mucous membranes. This occurs in many patients but has been sufficiently troublesome to warrant injection of sclerosing agents in only a few. Although the above inconveniences or disabilities have been moderately annoying to some patients, they have not been sufficiently serious to discourage our belief that near total sympathectomy is indicated for many disabled by hypertension.

CONCLUSION

Total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy in a substantial majority of a series of 113 hypertensive patients has apparently retarded and in some even arrested the hypertensive disease process.

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AN EVALUATION OF THE TREATMENT OF ESSENTIAL HYPERTENSION BY SYMPATHECTOMY*

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SYMPATHECTOMY has been done in this country for hypertension since 1933 and yet there is still lack of agreement as to its usefulness in this disease. In 1942, Grimsom¹ estimated that at least 3,000 patients had been treated in this way and by now this number must have more than doubled. Despite this large experience, varied opinions are still prevalent regarding the results obtained. It is the purpose of this communication to point out some of the reasons for the existing confusion and to review our own experience with 105 patients with essential hypertension treated by sympathectomy. Nephrectomy and removal of pheochromocytomas for hypertension will not be discussed.

It has been my contention that the final decision regarding the value of sympathectomy for hypertension will depend upon whether two purposes are accomplished by the operation, that is, relief of symptoms and prolongation of life. If a patient lives comfortably to a ripe old age, would it matter if the blood pressure were maintained at high, abnormal levels? Hence, a precise knowledge of these two factors would be enough for evaluation of the procedure. Obviously, one has only to compare a series of patients who have been operated on with a series of patients who have been treated by nonsurgical measures. Such comparisons lead to one conclusion at least, namely, that the operation brings about relief of symptoms in approximately 80 to 85 per cent of the cases. Therefore, this important question can be answered with assurance, but in regard to prolongation of life, there is much less agreement. The reasons for this lie in the fact that a number of different operations are still being done for hypertension, and classification of the patients is difficult because of our ignorance concerning the fundamental factors in the disease.

At present splanchnicectomy is being performed both above² and below³ the diaphragm. Ablation of the splanchnics and a portion of the sympathetic chain above and below the diaphragm at the same time, as advocated by Smithwick,⁴ is perhaps the most widely used procedure, also popular at several large clinics is a more extensive excision, first advised by Grimsom.⁵ Although the advocates of each operation believe in the superiority of the procedure of their preference, it is my belief that probably all operations accomplish the one essential—denervation of the adrenals. Widespread denervation increases the postural hypotension, however, there is no proof that this manifestation indicates benefit to the patient. This sequel to operation usually disappears within one year, yet three of our patients still have a small diminution in pressure in the erect position after three years. Some advocates of wide excision of the

* Read before the Southern Surgical Association, White Sulphur Springs, W. Va., December 9, 1948.

sympathetics maintain that the late elevation of blood pressure always is due to regeneration of these nerves. Although this may occur, the renewed high levels are probably more often a manifestation of the progressive changes in the vascular system which are taking place. Certainly little proof that regeneration is the cause has accumulated.

It has long been known that some hypertensive patients live comfortably with the disease for many years. Pereira⁶ recently pointed out, after following a large group of patients for years, that there is no constant correlation between a persistently high blood pressure and those complications which are usually regarded as following in its wake. Our ignorance of the fundamental pathologic process makes exact classification difficult, yet this is necessary if we are to predict the course of the disease in the individual patient. In order to do this, we must know the type of hypertension being operated upon and what can be expected if operation is withheld. At present, we must content ourselves with generalizations.

It is recognized that the prognosis in malignant hypertension is poor, regardless of treatment, and indeed, there are those who maintain that sympathectomy has little effect in prolonging life when this condition prevails.⁷ On the other hand, other surgeons claim results which, though not brilliant, are considered worthwhile.⁸ The same difficulty with classification is encountered when milder, less progressive disease is present, in fact, the future of these patients is less predictable than it is in the more severe types. The obvious need for a better selection of patients for surgical treatment has initiated investigations regarding blood pressure characteristics,⁹ effects of caudal anesthesia,¹⁰ spinal anesthesia and development of clinical rules.¹¹ We utilize high spinal anesthesia and the Sodium Amytal test routinely but have not been greatly impressed with their prognostic value.

The difficulties in comparing the results obtained in analogous series, one treated surgically and the other medically, are illustrated by reports of Keith, Wagener and Barker,¹² Peet^{2, 8} and Flaxman.¹³ The latter, who studied 244 patients fulfilling Peet's requirements for operation, noted that there were as many of his medically treated patients alive at the end of five years as there were in Peet's series of patients who had splanchnicectomy. Again, Peet reported 21 per cent of 143 patients with malignant hypertension treated by splanchnic resection alive at the end of five years, whereas in the Wagener-Keith series only one of 146 patients was living after five years of medical treatment. Some of these discrepancies probably depend on the variations in classification of the disease currently in use. Hence, it would be a distinct step in advance if a responsible professional body formulated an acceptable classification of hypertension which would be exact enough to permit comparison of patients treated by various methods.

Our own experience consists of 105 patients with hypertension who had bilateral thoracolumbar sympathectomy and splanchnicectomy prior to October, 1947 (Table I). The sympathetic chain and splanchnics were removed from the level of the seventh thoracic vertebra down to the third lumbar ganglion.

Sixteen other patients were excluded because either a nephrectomy also was performed or only unilateral sympathectomy was done. In each instance a careful study was made by our medical department and no patient was operated on who did not have symptoms and unmistakable evidence of progressive hypertensive disease. The youngest patient was 21 years of age and only three were 50 years or more. Heart failure and urea clearance of less than 50 per cent were considered contraindications to operation. Several patients had had cerebral vascular accidents. In reality, selection is based largely on the extent of the organic disease and resulting damage to the cardiovascular system and kidneys. Hence, the rules should not be too rigid except beyond certain limits. This is illustrated by our oldest patient, a man of 59 years, who had only moderate organic changes. Even though he had severe hypertension and incapacitating symptoms, the results of sympathectomy were excellent.

TABLE I—*Classification of 105 Cases of Essential Hypertension Treated by Sympathectomy*

	Cases	Per Cent
Group I	8	7.6
Group II	63	60.0
Group III	34	32.4
Total	105	100.0

The cases were classified into three groups. Group I consisted of young persons with somewhat variable hypertension, little cardiovascular disease, normal renal function and minimal retinal changes and symptoms. Group II usually included older persons with progressive hypertension, definite cardiovascular disease, often some reduction in renal function and moderate to

TABLE II—*Blood Pressure Response of Followed Patients in Group I
Average Preoperative Blood Pressure 176/112*

Case	Blood Pressure in Mm/Hg			Years Postoperative
	1	2	3	
1	155-100	180-100	170-120	
2	190-110	190-110		
3	140-90	160-110		
4	140-94	150-90	150-90	
5	150-90	150-100		
6	160-105	140-90		

severe retinal changes and symptoms. In Group III the patients had a fixed diastolic pressure above 140 millimeters of mercury, cardiovascular disease, reduction in renal function, severe retinal changes and acute symptoms.

There were four postoperative deaths in the entire series. Data on the patients' course after operation were obtained by follow-up examinations which usually included an electrocardiogram, urea clearance test and examination of the optic fundus.

It is believed the principal interests of this study are the results obtained at the end of one year. This period is admittedly too short for a comprehensive evaluation, but it is generally conceded that the results become less favorable

with the passage of time and hence the optimum should be reached about one year after operation. By establishing such a yardstick, the information thus obtained might profitably be compared with data embracing longer periods.

There were eight patients (7.6 per cent) in Group I, two of whom could not be traced. As shown in Table II, in only two patients could the blood pressure be considered normal one year after operation. Two other patients obtained little reduction in blood pressure. At the end of two years, again only two had pressures that could be considered normal. There were no deaths in this group and all patients obtained satisfactory symptomatic relief.

TABLE III—*Followed Patients in Group II*

Follow up	1 yr	2 yr	3 yr
Living	40	18	8
Dead	3*	0	0
Total	43	18	8
Per cent of patients followed who are living	93	85	72

* 2 were postoperative deaths

Group II contained 63 patients, only 40 of whom were followed for one year (Table III). There were two postoperative deaths and only one other death during the year. We are not aware of any deaths in the second and third years, but the number of patients followed becomes smaller and more time will be required to evaluate this group over a longer span. In only 40 per cent of the patients was the blood pressure response good at the end of the

TABLE IV—*Results in 40 Patients in Group II Followed One Year*

	Cases	Per Cent
Blood pressure response		
Good (almost normal or normal)	16	40
Fair (reduction but levels definitely abnormal)	12	30
Poor (little significant reduction)	12	30
Definite improvement in retinal changes	12	30
Definite improvement in cardiac status	14	35

first year, but most of these still had manometric readings which must be considered abnormal (Table IV). Twelve (30 per cent) had a definite reduction in blood pressure but the levels remained abnormally high. Another 12 (30 per cent) were little improved from this standpoint. Of the 40 patients, 12 exhibited definite improvement in the retinal changes and 14 showed unmistakable improvement in the cardiac status.

There were 34 patients (32 per cent) having malignant hypertension (Group III), of whom 28 have been followed for one year (Table V). Six of these died, two of them postoperatively. Although 78 per cent of the patients followed were alive at the end of one year, this figure was reduced to 23 per cent at the end of three years. Of the 22 alive at the end of the first year, only two had near normal blood pressures, but seven had obtained a fair response (Table VI). Six of the 22 showed improvement in retinal changes.

The symptoms accompanying hypertension do not always bear a relationship to the height of the blood pressure. This is true both before and after operation. In our patients, symptoms were relieved in over 80 per cent of the patients even though at times there was not a concomitant fall in blood pressure. Many observers have described improvement in renal function following sympathectomy, thus, Peet² claimed that "45 per cent of the patients with abnormal urea clearance have returned to normal and 44 per cent with impaired water concentration have marked improvement." Similar improvement in our patients was not evident.

Reports now available reveal numerous discrepancies when compared with our experience. Again, Peet² stated that 20.3 per cent of his living patients

TABLE V—*Followed Patients in Group III*

Follow up	1 yr	2 yr	3 yr
Living	22	9	3
Dead	6*	3	1
Total	28	12	4
Per cent of patients followed who are living	78	50	23

* 2 were postoperative deaths

have maintained normal blood pressures following splanchicectomy for five to twelve years, whereas Smithwick⁹ noted improvement in blood pressure in 66 per cent of a large series followed for one to five years. A comparison of these results with our experience makes it clear that our results at the end of one year are less satisfactory even though the operation was adequate according to the criteria of both Peet and Smithwick. Numerous other reports could be cited to illustrate the diverse interpretations of the results following sympathectomy.

TABLE VI—*Results in 22 Patients in Group III Followed One Year*

	Cases
Blood pressure response	
Good	2
Fair	7
Poor	13
Definite improvement in retinal changes	6

SUMMARY

A more exact and uniform classification for hypertension obviously is needed to enable a better selection of patients as well as to allow a better interpretation of the results. We have been interested particularly in the results after one year because it is believed that these represent the optimum and therefore, they can be used as criteria for measuring remote end results.

The present study confirms the ability of sympathectomy to relieve hypertensive symptoms in more than 80 per cent of well-selected patients. Our experience has not provided a definite answer as to whether life is prolonged

The operation is probably justifiable for relief of symptoms alone, although it is our impression that many of the patients having sympathectomy live longer than they would have if operation had not been performed

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DISCUSSION—DR WINCHELL MCK CRAIG, Rochester, Minn Doctor Grimson and Doctor Penick have brought us up to date with regard to the surgical treatment of hypertension, which I attempted to do before this group two years ago Although Doctor Grimson presented an excellent argument for total sympathectomy, I still wonder whether this is not a pretty radical procedure for some of the patients suffering from hypertension and whether we should not reserve it for a special group

Some of us who have been performing surgical operations for hypertension for a period of years have had a tendency to think of progressive hypertension very much as we do other types of malignancy, that is, that any patient who has hypertension which fails to respond to medical measures and progresses should have surgery However, if our follow-up studies have been of any value, they indicate that some patients who have the more advanced hypertension have irreversible changes which cannot be altered by surgery Although it is true that in some cases in the early stages remissions may occur, in the group of cases which we have followed, in which hypertension Groups II or III has developed in a short period, the hypertension can be controlled by surgical procedures It is controlled from the standpoint of blood pressure and appearances of the fundi, as well as alleviation of symptoms

So many factors are present in the etiology of progressive hypertension that we must recognize the disease in its early stages if we expect to approximate the five-year cures obtained by the surgical treatment of malignant lesions We cannot overlook the fact that Ayman pointed out a definite hereditary factor, which has been developed by Hines and Brown, and that entire families with a bad heredity have hypertension in spite

of all types of treatment. There is no question but that surgical procedures in this group have changed the prognosis in a certain number of cases and these results have been obtained with a less radical procedure than is outlined by Doctor Grimson.

I think we are all interested in this problem from the standpoint of a minimal amount of surgery for a maximal amount of benefit. If total sympathectomy is indicated in a certain group of cases and it can be proved that these patients are comfortable, are able to return to work and enjoy life in general, then it can be endorsed. If, on the other hand, some of the patients are not comfortable or able to return to gainful occupations, even though the blood pressure is lowered, the question will remain in some of our minds as to whether a less radical procedure would not have served the purpose.

The physiologic effect of the removal of all or a portion of the sympathetic nervous system needs to be evaluated, not only from the standpoint of the effect on the blood pressure but the over-all picture of the disease, and it is such reports as we have heard today which help us to evaluate the treatment of hypertension by surgery on the sympathetic nervous system.

DR FRANK H. LAHEY, Boston: I always feel embarrassed in discussing papers on hypertension because I do not know anything about it. As I said when I discussed Doctor Craig's paper last year, it does seem that this is so important that all data available should be presented in order that we may have as much information as possible upon which to make decisions as to the value of the principles involved in the surgical treatment of hypertension, and in evaluating methods. Doctor Poppen presented me with figures from the Clinic in which it has been possible to compare the results in 100 cases, as I reported two years ago for him, report on which was published by Doctor Poppen and Doctor Lemmon in the Journal of the American Medical Association. In these cases the resections were from the tenth thoracic through the second lumbar, and from the sixth thoracic to the second lumbar. This group can now be compared with 275 cases in which all the resections were from the fourth thoracic through the second and third lumbar. These cases have been followed by Doctor Evans and Doctor Bartels in the medical department, and it will be of interest, particularly in the light of these two papers, to present the comparison of some of the results in the latter group of cases.

We have also been interested, as we have watched these cases, to observe that the effects on patients with Group III hypertension (Keith-Wegener formula) have been striking in the degree of improvement in the more extensive resections, as compared with less radical ones. In the earlier group there was only 4 per cent definite improvement, as compared with 44 per cent in the latter group. In Groups I and II it has been of interest to compare the groups. While these figures are only approximate, I have always remembered the report of the first group in terms of satisfactory, fair, and unsatisfactory.

In the first group, satisfactory results were obtained in roughly 50 per cent, fair results in 25 per cent, and unsatisfactory results in 25 per cent. The figures in the latter group have changed to 70 per cent satisfactory, 20 per cent fair, and only 10 per cent unsatisfactory. Some of the other results have also been interesting. In 15 patients with angina, 60 per cent were relieved. On the other hand, none of these had serious coronary disease.

There was improvement in 42 per cent of 50 patients who had abnormal electrocardiograms. Renal function tests were improved in 58 per cent of 55 patients who had had one or more impaired tests before operation. Retinal vascular change improved in 66 per cent of 170 patients. This should settle the question as to whether the more radical procedure should be done. The mortality in the first group was 0.5 per cent and in the second group is still 0.5 per cent. This is interesting because all, or practically all, have been done by one surgeon (J. L. P.). We should be loath to consider this type of operation, with its prolonged, uncomfortable convalescence, as a prophylactic operation for benign hypertension, but urge it on patients under the age of 50, with spastic, exudative and hemorrhagic retinal arterial changes, moderate cardiac damage and signs of early nephrosclerosis.

I have often looked over Doctor Poppen's shoulder and have seen regeneration around the silver clips placed on the sympathetic nerves in previous operations in the hope that they might retard the progress or rate of growth. It is true that the splanchnic usually originates at the sixth level, and may in the fourth, and he feels because of this, that with removal at the fourth there is less likelihood of regeneration of the splanchnic branches. I present these figures so that they may be available to everyone.

DR JOHN FAIRON, Worcester, Mass. During the adolescence of any operation, especially one so important as this, it seems advisable to accumulate quickly the scattered reports of complications, tragedies and other unexpected results. There is nothing I can do to express my gratitude to your Association for your hospitality better than to tell you about a patient whom I would rather forget.

Some years ago we had a patient who, following the unexpectedly high climb of a spinal anesthetic had minor but permanent effects of cerebral anoxia. That made us conscious of the complications which might occur from hypotension during the operation for hypertension. Before starting to do sympathectomies we tried various methods, reported and otherwise, of controlling temporary hypotension, including a pressurized suit such as is used by aviators to prevent blackout. In spite of this awareness we had a total paraplegia at the eleventh dorsal in a patient aged 50 with severe malignant hypertension. The operation was a Smithwick, the anesthesia nitrous oxide-ether, and she awoke from the anesthesia with a paraplegia which still persists. The spinal fluid and its pressure were normal. Was it an accident, was it a surgical error? If an accident, how likely is it to occur with this operation? We think it likely to be from temporary ischemia or thrombosis of vessels, especially the anterior spinal artery. During operation this patient, whose vascular system was accustomed to a pressure of 300, had a pressure of less than 60 for several minutes despite the inflow of saline and blood, started before operation. She was not subjected to any of the experimental methods we have used to prevent hypotension, so these cannot be blamed.

DR KEITH S. GRIMSON, Durham, N. C. (closing). The interest of the discussors is appreciated. Several have mentioned relationship of causes of hypertension to results of sympathectomy. We have postulated neurogenic mechanisms as an important initiating and perpetuating cause of clinical hypertension. Results of near total sympathectomy as presented would seem to confirm this hypothesis at least for many of the patients treated. There are, as described in the manuscript, several other important causes of hypertension that might not respond to surgery. Persistence of these other etiologic factors might account for some of our failures.

Experiences with splanchnicectomy performed in another series have been less satisfactory than those reported for near total sympathectomy. These results agree with those for splanchnicectomy reported by Doctor Penick and we agree with his statement that benefits obtained by this operation are often equivocal. Doctor Craig has well stated that the problem of hypertension is large and that surgery is only one approach. Sympathectomies are uncomfortable and temporarily disabling. Also they are performed with some risk of operative mortality. Even though mortality rates can be reduced and the proportion of good results increased by operating upon patients with milder forms of the disease as he suggested, we cannot agree with this practice. It is our opinion that surgery is not indicated for patients with mild hypertension and also that, by using near total sympathectomy, one may aid patients with more serious forms of the disease at an only slightly increased risk.

Doctor Lahey's excellent report of results obtained by Doctor Poppen is very interesting. His statistics would seem to indicate that extension of splanchnicectomy upward to include denervation of thoracic somatic segmental distribution as high as that supplied by the fourth thoracic ganglia has improved results of splanchnicectomy. From the physiologic point of view this seems improbable. There are two explanations of improvement of results which should be evaluated. One is that each time the technic of splanchnic-

nicectomy is changed, results early and perhaps temporary must be contrasted with the later results of the earlier series. The second explanation is that most surgeons using splanchnicectomy have with increasing experience tended to limit their selections of patients to milder forms of the disease. Doctor Poppen's excellent studies when reported in detail will undoubtedly evaluate these factors. In the meanwhile, extension of his operation to include the remaining upper three ganglia and stellate would add thoracic and cerebral visceral denervation and interruption of adrenergic pathways to head, neck, shoulders, arms, and upper chest. This would permit comparison of results of their then near total sympathectomy with results of their now extensive splanchnicectomy. Such a comparison would be welcomed.

We are in entire agreement with Doctor Waldron that trial of different operations is good. Up to the present time each surgeon extending sympathectomy has continued using the more extensive denervation, and no one to my knowledge has reverted to the earlier more limited procedures.

Dr. Fallon has described an instructive and important danger, that of hypotension during operations upon patients with cardiovascular disease. Occurrence of shock during operation may cause irreparable damage to the central nervous system or the heart. Marked reduction of blood pressure can be avoided by routinely using blood transfusions, intravenous fluids, and peripherally acting vasoconstrictors during operation. Also, it is our opinion that use of the transthoracic approach rather than the posterior dissections through muscles of the back, markedly decreases the operative time and reduces trauma and blood loss, thus diminishing danger of surgical shock. The transthoracic approach decreases magnitude of operation and at the same time permits better visualization of the sympathetic chain, and more extensive removal.

PRESACRAL ENTEROGENOUS CYST*

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THIS PAPER presents a case of enterogenous cyst located in the presacral area. It is also our desire to present each case of histologically proved enterogenous cyst that has been reported in the literature as occurring below the peritoneal reflexion.

Enterogenous cyst is a term applied to congenital cysts which have their origin from some portion of the digestive tube. The literature is filled with reports of these cysts arising from the stomach and from the small and large bowel, but reports of cases involving the rectum are scant. It is our desire to report only the cases that have arisen ventral to the sacrum and below the peritoneal reflexion.

Ten reported cases that carry histologic proof of enteric origin have been found in the literature. To this number we wish to add the following case report.

CASE REPORT

Mrs. L. L., a white woman age 33, consulted us on May 12, 1948, complaining of indigestion of two years' duration. Her history was suggestive of duodenal ulcer. There was no complaint of any rectal difficulty, but in the course of physical examination a smooth, fluctuant tumor was felt posterior to the rectum and in close approximation to the coccyx. The tumor was slightly movable in all directions and was not excessively tender to pressure. The finger, on rectal examination, could reach the dome of the tumor and its size was estimated to be that of an English walnut. Proctoscopic examination revealed only a smooth rectal wall over the tumor. Air contrast roentgen-ray studies of the rectal ampulla showed no tendency for the tumor to protrude into the posterior rectal wall. Roentgen-ray studies of the sacrum revealed an indefinite soft tissue mass just ventral to the coccyx. The tip of the coccyx was bent forward at a right angle from the lower sacral segment. All laboratory examinations fell within normal limits except that stool examinations were positive for occult blood. Roentgenographic visualization of a duodenal ulcer confirmed a typical ulcer history.

She was placed on medical management for the ulcer, and the systemic response was rapid. During the course of her early ulcer management we had time to become familiar with lesions occurring in the presacral area by study of the literature. A case report by McLanahan and Stone³ made the tentative diagnosis of enterogenous cyst tenable in our case. The patient readily agreed to the removal of the tumor. Because of the close approximation of the tumor to the posterior rectal wall, it was thought wise to administer sulfasuxadine for ten days prior to surgery.

OPERATION

On June 8, 1948, the tumor was removed through a posterior three inch midline incision from the anus to the coccyx. It was necessary to remove the distal segments of the coccyx to uncover the tumor in its entirety. With a finger against the tumor from the inside of the rectum, the mass was dissected free from its attachment to the posterior rectal wall, and after enucleation, the gloved finger could be seen clearly through the bowel mucosa. No tissue being available for obliteration of the space occupied by the

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tumor, the wound was dusted with sulfathiazole and a soft rubber drain inserted beneath the skin. Drainage persisted for ten days, when healing became complete.

PATHOLOGIC DIAGNOSIS

Gross Examination The specimen consisted of a well-encapsulated, thin-walled cyst measuring $2\frac{1}{2} \times 1\frac{1}{2}$ centimeters. Cut section revealed the cyst to be filled with thick, mucoid material. The wall was lined with a pink, soft, mucosalike tissue and measured 0.2 centimeters in thickness.

Microscopic Examination Sections were made from many different areas of the cyst, and were stained with hematoxylin-eosin, azocarmin and mucicarmin, respectively.

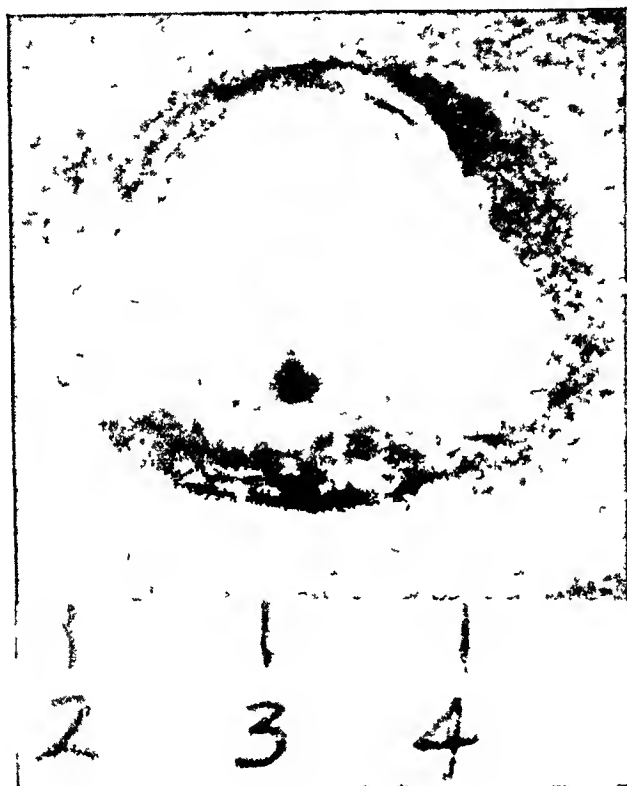


FIG 1—Gross appearance of the enterogenous cyst

Sections stained with hematoxylin-eosin showed the cyst wall as built of the following layers: an epithelial layer and a sub-epithelial layer, loosely arranged, containing small vessels, cell formations like plasma cells, large mononuclear lymphocytes and wandering cells. This layer was followed by two coats of tissue consisting mainly of smooth muscle layers. In addition to these muscle layers, collagenous and reticular connective tissue were present, as indicated by azocarmin stain.

The outermost layers of the cyst were indistinct, and peritoneum could not be demonstrated. Between the outer and inner layers, we found bundles of nerves and in one instance a collection of ganglion cells. By this description the tissue is that of intestinal wall if the epithelium presents the characteristic features of bowel mucosa. Under normal conditions, the mucous membrane of the intestine consists of high columnar, mucus-secreting cells arranged to a certain pattern. In our case, the covering epithelium also consisted of several layers of squamous or transitional epithelium. The cells in the squamous area were in several layers, the lower one more columnar in type, while the uppermost layer showed a more balloonlike cytoplasm. There were areas where this cell layer did not

consist of squamous epithelium but of mucus-producing columnar epithelium, proved by the use of mucicarmum stain

Stains with iron hematoxylin and with mucicarmum prove furthermore the presence of a cuticulum. Cells of this type are met with in the whole intestinal tract from the cardia to the anus.

Practically all layers characteristic for intestine were demonstrable, namely, mucus-producing columnar epithelium, smooth muscle layers with vessels and nerves. The presence of squamous epithelium is attributed to the effect of metaplasia.

Diagnosis Enterogenous cyst

TABLE I

Author	Year	Author's Diagnosis	Pathologic Diagnosis	Age and Sex	Symptoms	Treatment
Middledorpf	1885	Cyst of postanal gut origin	Small loop of vestigial intestine	1 yr, F		Posterior excision by Kraske
Ballantine	1932	Cyst of postanal gut origin smaller of adenocarcinoma	Cyst of intestinal origin with early adenocarcinoma	38 F	Pain in left buttock	Posterior excision
McLanahan and Stone	1934	Presacral enterogenous cyst	Enteric cyst	48 F	Lump in rectum	Posterior excision
McLanahan and Stone	1934	Presacral enterogenous cyst	Enteric cyst	1 mo M	Vomiting and constipation	Aspiration and subsequent posterior excision
Thomason	1934	Cyst of postanal gut	Cyst of intestinal origin	34 F	Pain, draining sinus	Repeated posterior excision
Raven	1935	Cyst of postanal gut	Cyst lined with stratified columnar and ciliated epithelium	2½ mo, F	Acute obstruction	Demonstrated at autopsy
Guis and Stout	1938	Cyst of vestigial gut	Cyst of intestinal origin	26 F	Pain and pressure in rectum	Intrarectal marsupialization
Guis and Stout	1938	Cyst of vestigial gut	Cyst of intestinal origin	36 F	None found on routine exam	Posterior excision
Ladd and Gross	1940	Duplication of rectum	Cyst of intestinal origin with mixed mucosa	6 mo, F	Recurrent obstruction	Repeated aspiration and subsequent posterior excision
Custer, et al	1946	Enterogenous cyst involving rectum	Enterogenous cyst	29 M	Symptoms of bladder pressure	Excision by laparotomy

REVIEW OF LITERATURE

We have been able to find ten cases of histologically proven presacral enterogenous cysts reported in the literature (Table I)

Middledorpf,¹ in 1885, was the first to describe a presacral cyst of intestinal origin. The patient was a one-year-old female, and when the cyst was removed by Kraske, it was found microscopically to have all the structure of intestinal wall. Diagnosis cyst of postanal gut origin.

In 1932, Ballantyne² reported a presacral cyst in a female of 38 years. The cyst contained 475 cc of fluid and was removed by posterior excision. Microscopically, the cyst was lined with columnar epithelium. Goblet cells secreting mucin were present. There was a small area showing adenocarcinoma. Diagnosis: cyst of postanal gut with area of adenocarcinoma.

In 1934, McLanahan and Stone³ described two cases of presacral enterogenous cyst. The first case was a woman of 48 years who complained of a lump in the rectum which at times would protrude from the anus but was easily reduced. Digital examination revealed a small cystic mass lying about two inches within the anal orifice and situated between the posterior wall of the



2—Low power microphotograph of cyst wall demonstrating the different layers of epithelium, subepithelium, and muscularis

rectum and the coccyx. The mass was about the size of a walnut, was fluctuant, freely movable and not tender. Doctor Stone removed the tumor by posterior excision after the coccyx was resected. The mass was dissected from the posterior rectal wall, to which it was closely attached. Microscopic examination of the cyst wall showed tall columnar epithelium of mucus-secreting type. The submucosa was composed of longitudinal and circular muscular layers covered by a layer of serosa. Diagnosis: enteric cyst.

The second case reported by McLanahan and Stone was in a one-month-old male infant with intestinal obstruction from a mass filling the rectum. The mass was thought to be an intussusception, but on exploration of the abdominal cavity, a fluctuant mass the size of a golf ball was found below the peritoneal reflexion. The abdominal wound was closed, and on the following day the tumor was aspirated by needle entering the skin one inch to the right of the

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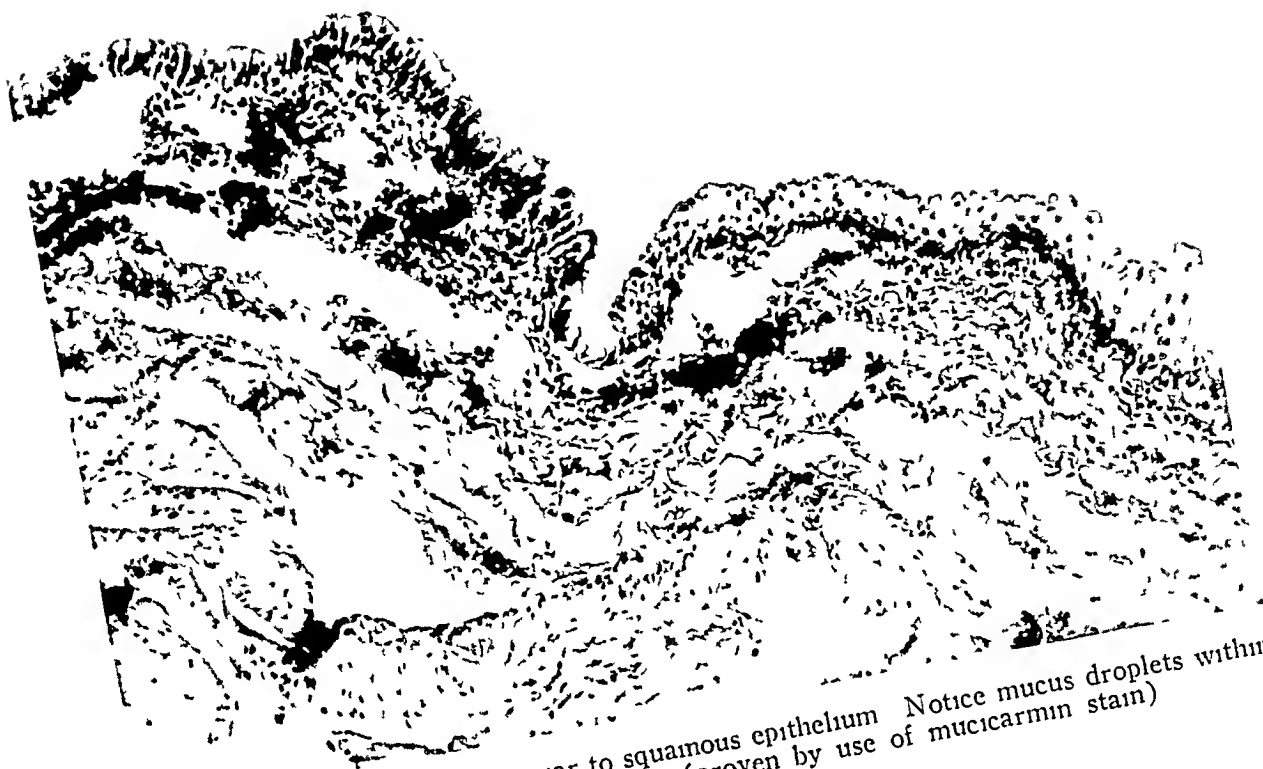


FIG 3—Metaplasia from columnar to squamous epithelium. Notice mucus droplets within the cytoplasm of columnar cells (proven by use of mucicarmin stain)

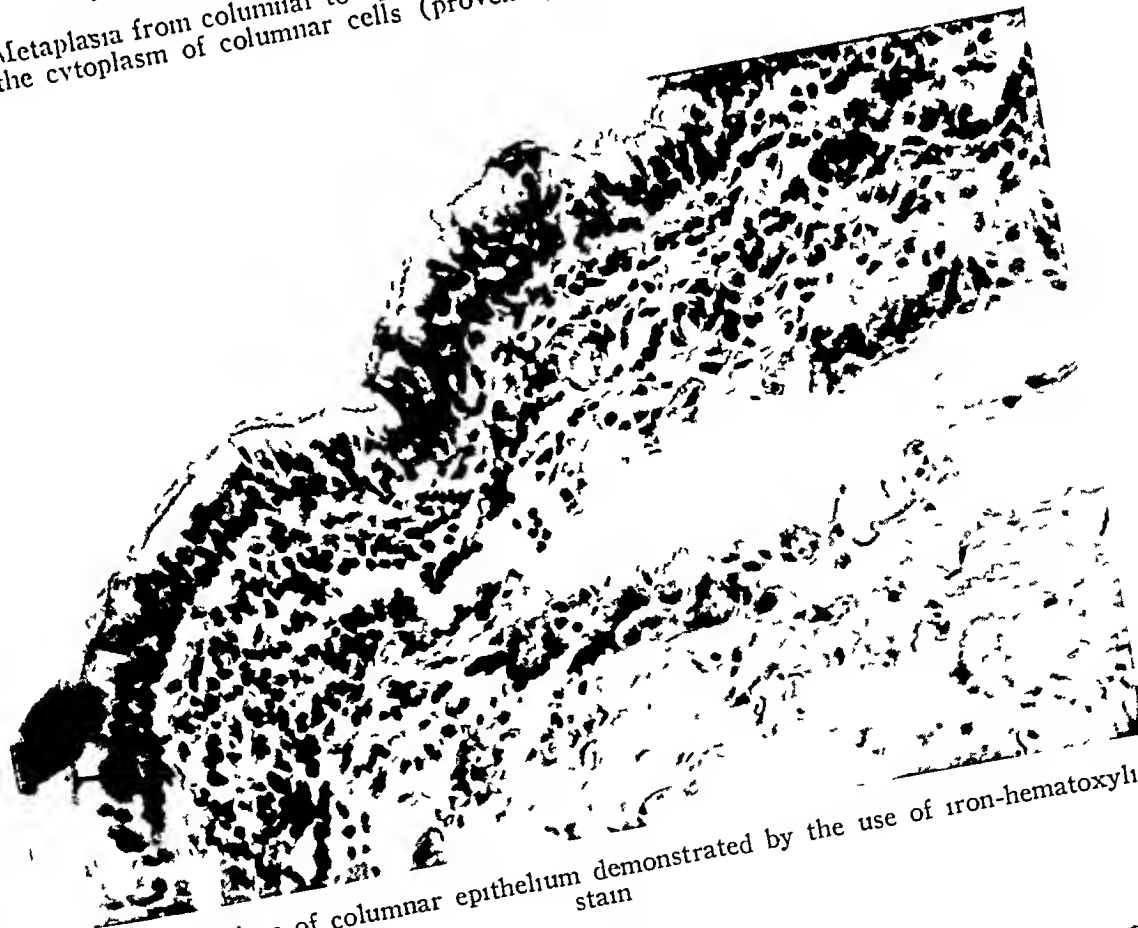


FIG 4—Cuticulum of columnar epithelium demonstrated by the use of iron-hematoxylin stain

posterior margin of the anus. Twenty-five cc of cloudy fluid were withdrawn, and the obstruction was temporarily relieved. The cyst was aspirated on five occasions in the next month, and the condition of the baby so improved that posterior excision of the cyst was performed. The microscopic sections showed a well-defined mucosa lined with columnar epithelium of mucus-secreting type. The outer wall was composed of two circular and longitudinal muscle layers covered by serosa. Diagnosis: enteric cyst.

Thomason,⁴ in 1934, reported a case of sacro-coccygeal cyst of the postanal gut. His patient was a 34-year-old woman with a draining sinus near the tip of the coccyx which had been present since a mass in that area was incised and drained several years before. The sinus tract and the cyst were removed by posterior excision. Microscopic examination showed the wall of the cyst to be made up of columnar epithelium of the mucus-secreting type, Peyer's patches and two layers of smooth muscle. Diagnosis: postanal gut cyst.

Raven's⁵ case, reported in 1935, was a 2½-month-old female who was acutely obstructed by a recto-rectal cyst. The condition was thought to be an intussusception, and laparotomy was performed. At autopsy the mass was removed and microscopic sections showed the cyst to be lined with several layers of epithelium, the innermost being ciliated columnar epithelium. Diagnosis: cyst of postanal gut.

Guis and Stout⁶ reported two cases in 1938. The first was a 26-year-old female who complained of rectal pain and pressure. A palpable mass posterior to the rectum was thought to be an abscess. An intrarectal incision was made and the tumor wall marsupialized from within after removing a part of the wall. Pathologic examination showed stratified and columnar epithelium with mucin secretion and smooth muscle layers. Diagnosis: cyst of vestigial gut origin.

The second case of Guis and Stout⁶ was a 36-year-old female with a cyst in the postero-lateral rectal wall found on routine rectal examination. Posterior excision of the cyst was done and the pathologic examination showed smooth muscle and a mucosa which was composed of stratified squamous and ciliated columnar epithelium tending to form glands. Mucin was present. Diagnosis: cyst of vestigial gut origin.

Ladd and Gross⁷ reported one case in 1940. They prefer the term "duplication of a part of the alimentary canal," but also use the term enterogenous cyst. Their patient was a female, age 6 months, who had recurrent bowel obstruction due to a presacral mass. This tumor was removed by posterior excision. The sections of the cyst wall showed mucosa, submucosa and the muscle layers characteristic of intestine. The mucosa showed mixed types of glands, some of colon and some of gastric type. Diagnosis: duplication of rectum.

Custer, Kellner and Escue⁸ report one case in 1946. Their patient was a 29-year-old man complaining of pressure in the pelvis, epigastric pain and a decrease in urinary bladder capacity. Rectal examination disclosed a cystic mass which filled the pelvis. This mass was removed through a low midline

incision. Its attachment was to the anterior rectal wall. Pathologic examination showed the cyst wall to be made up of tall columnar mucus-secreting epithelium and a well-defined layer of smooth muscle. Diagnosis: enterogenous cyst.

ETIOLOGY

Three theories have been advanced to explain the presence of enterogenous cyst.

Middledorpf,¹ in reporting his case of enterogenous retro-rectal cyst in 1885, felt that the origin of the cyst was in the vestigial postanal gut. Five of the other authors reporting their cases chose to believe that this theory best explains the presence of the cyst in the midline between the coccyx and the rectum.

The diverticular theory of cyst origin is based on the work of Lewis and Thynge,⁹ who demonstrated that diverticula occur frequently in all portions of the digestive tube of the embryo. These may become occluded at the neck and the cyst results.

A third theory, known as the sequestration theory, suggests that a group of cells becomes pinched off from the primordial intestinal tube and undergoes subsequent development outside the lumen of the intestine.

PATHOLOGY

Although the term "enterogenous" or "enteric" cyst has become accepted when applied to these tumors, they are perhaps more accurately named "duplications of the alimentary tract" as suggested by Ladd and Gross.⁷ Their term is actually the requirement for pathologic diagnosis of these cysts.

As Ewing¹⁰ pointed out, the most variable component is usually the mucosal lining, which may show cylindrical, cuboidal, stratified or flat epithelium. The degree of tension within the cyst, together with the amount of inflammatory reaction, produce many variations in the type of mucosa. Ladd and Gross,⁷ in reporting their case of presacral cyst, pointed out that the mucosa may be typical of that segment of the bowel to which it is adjacent or it may be typical of some bowel segment far removed from the cyst. The mucosa may be mixed, as in their case, showing large bowel and gastric mucosa.

The presence of intestinal mucosa, smooth muscle layers, nerve bundle and serosa establish the origin of the cyst to be enteric. The serosal layer is usually absent when the cyst is presacraly located.

TREATMENT

The treatment in reported cases has been aspiration, incision and drainage through the rectum, marsupialization and removal by intra-abdominal approach or posterior excision. All authors advise removal as a necessity in some cases and as a guard against malignant degeneration. The removal of the cyst usually can be accomplished by the removal of the coccyx in a posterior approach.

We wish to acknowledge our indebtedness to Dr. Phillip R. Rezek for the pathologic report in this case.

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DISCUSSION—DR G V BRINDLEY, Temple, Texas I am sure all of you have enjoyed this excellent paper, for it is a most interesting presentation of one of the infrequent tumors which originate in and ventral to the sacrum The caudal area is the location for many pathologic types of cysts, tumor, sinuses and fistulas which usually arise from vestigial embryonic tissue

Some seven years ago, within a period of 14 months I encountered three neoplasms which originated ventral to the sacrum It was my privilege to present these cases before this Association four years ago One of these growths was a chordoma, another was an ependymal cell glioma, and the third was a large dermoid cyst Since statistical data show that most patients with chordoma do not remain well, it was believed that it probably would be of interest to report at this time that the patient who had the chordoma is well and apparently free of disease It is now eight years since the neoplasm was removed

May I mention three facts worthy of emphasis pertaining to tumors of this region The first is that diagnosis of most of these neoplasms depends upon a careful vaginal and/or rectal examination Certainly no physical examination is complete unless these examinations are performed Another fact deserving comment is that these tumors are removed only by complete removal To attempt to cure a cyst of this region by incision and drainage usually results in secondary infection and a persisting sinus Furthermore, adequate exposure is essential for removal of these lesions The complete excision of a growth of this region is facilitated by the proper approach, which is obtained by an incision over the sacrum and coccyx extending to near the anus The patient should usually be in the Kraske position The coccyx and as much of the sacrum below the sacroiliac articulation as is necessary for adequate exposure of the neoplasm should be removed, together with the muscles and nerves of this region

It should be appreciated that the segment of the sacrum below the sacroiliac articulation, together with the coccyx and all the sacral nerves except the first and second can be removed without severe disability being incurred by the patient

Again let me congratulate the essayist upon this fine presentation

DR HARVEY STONE, Baltimore I want to thank Doctor Perry for putting this case in the record, because it seems to me that, in view of his study of the literature to date, anyone encountering such a condition as this should record it, because of our scanty infor-

mation about these cysts. At the same time, I feel sure that his finding only 11 such tumors in the literature bears no real relationship to the frequency of occurrence, because there must be many cases unrecorded. While the total figures involved are too small to be of statistical significance, it is remarkable that of 11, nine were in females. Whether that means anything I am not prepared to say. Four patients presented themselves with symptoms of intestinal obstruction, of greater or less degree. This is highly significant, it means that the tumor must have slowly grown to a size that made it mechanically obstructive over a considerable period of time, ordinarily these tumors do not cause obstruction.

I want to repeat what was said about the surgical approach. I feel first that complete removal is the only satisfactory treatment. Second, that the proper approach is from below and behind, with a vertical incision posterior to the anus, with removal not of the coccyx alone but of a sufficient amount of the sacral body to get adequate exposure of the tumor. The amount to be removed is to be determined by the size of the mass. And, finally, it is important in doing the operation not to perforate into the rectum and not to damage the sphincter.

ANNOUNCEMENT

Beginning with the first issue of Volume 130 of the ANNALS OF SURGERY, July, 1949, the Editorial Board plans to publish signed editorials in each monthly issue. The editorials will be written (to begin with) by members of the Editorial or Advisory Boards. These editorials are not intended to be summaries of recent advances in surgery, nor are they intended to be short original articles on scientific subjects. They will, rather, express the opinions of the authors on matters of general interest to the surgical profession which do not ordinarily appear in scientific articles.

JOHN H. GIBBON, JR., M.D.,
Chairman, Editorial Board

PHILADELPHIA ACADEMY OF SURGERY

THE SAMUEL D. GROSS PRIZE

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Essays will be received in competition for the prize until
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The conditions annexed by the testator are that the prize "shall be awarded every five years to the writer of the best original essay, not exceeding one hundred and fifty printed pages, octavo, in length, illustrative of some subject in Surgical Pathology or Surgical Practice founded upon original investigations, candidates for the prize to be American citizens "

It is expressly stipulated that the competitor who receives the prize shall publish his essay in book form, and that he shall deposit one copy of the work in the Samuel D Gross Library of the Philadelphia Academy of Surgery, and that on the title page it shall be stated that to the essay was awarded the Samuel D Gross Prize of the Philadelphia Academy of Surgery

The essays, which must be written by a single author in the English language, should be sent to the "Trustees of the Samuel D Gross Prize of the Philadelphia Academy of Surgery, care of the College of Physicians, 19 South 22nd Street," on or before January 1, 1950

Each essay must be typewritten, distinguished by a motto, and accompanied by a sealed envelope bearing the same motto, containing the name and address of the writer. No envelope will be opened except that which accompanies the successful essay

The Committee will return the unsuccessful essays if reclaimed by their respective writers, or their agents, within one year

The Committee reserves the right to make no award if the essays submitted are not considered worthy of the prize

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